UNIVERSITY OF LONDON
HEATH CLARK LECTURES, 1934
delivered at
The London School of Hygiene and Tropical Medicine

MALARIA IN EUROPE

AN ECOLOGICAL STUDY

BY

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OXFORD UNIVERSITY PRESS
LONDON : HUMPHREY MILFORD
1937

OXFORD UNIVERSITY PRESS
AMEN HOUSE, E.C. 4
London Edinburgh Glasgow New York
Toronto Melbourne Capetown Bombay
Calcutta Madras
HUMPHREY MILFORD
PUBLISHER TO THE UNIVERSITY

PRINTED IN GREAT BRITAIN

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NOTE

No exhaustive bibliography has been attempted, but references to most of the recent additions to our knowledge of malaria are given in footnotes which can be traced under subject and author in the index.

A glossary giving definitions of the scientific terms most frequently used will be found at the end of the book.

FIG. 1. THE RUINS OF NINFA IN THE PONTINE MARSHES
The starting-point of our discussion. Were the forces which destroyed it social or entomological?

PREFACE

THIS is not in any sense a text-book on malaria. It is a discussion of the newer findings in malaria and the way these are changing our ideas of what endemic malaria is, why it persists, and how it can be attacked. It is the sort of talk which goes on among malariologists when they get together in trains or after meetings, but rarely finds its way into print in connected form. Much of it may be dignified as 'present theory', a good deal is hypothesis, some of it is out-and-out speculation.

The discussion is based almost entirely on European experience. About ten years ago (1925) the Rockefeller Foundation, in collaboration with the Italian Health Department, founded the Malaria Experiment Station in Rome, and soon after, similar centres for field study were created in Greece, Bulgaria, and Spain. The co-operation of Professor Martini of Hamburg and Professor Swellengrebel of Amsterdam was obtained for the observation of northern European anophelism and malaria. After preparatory studies, these centres have been engaged in large-scale experiments with every fundamental measure which seems to hold out possibilities of success in combating malaria. Out of all this work there has gradually emerged a uniformity of opinion regarding malaria control, the more noteworthy because of the diversity of the problems which had to be analysed and solved. Since this belief, held in common by almost all of us who are actively struggling with malaria in southern Europe, has not always been in conformity with the doctrines of the so-called European school of malariology as set forth, let us say, in the Second Report of the Malaria Commission of the League of Nations, one of my principal objects will be to show on what grounds this point of view is based.

This book is made out of the material gathered together for the Heath Clark Lectures, given at the London School of Hygiene and Tropical Medicine in December 1934. When I was invited to give these lectures I was admonished to keep the subject-matter non-technical and to try to make it interesting to 'ordinary physicians and intelligent laymen'. This has also been my endeavour in writing the book.

A good deal of the illustrative material, drawn from field studies and campaigns in many countries, and in large part unpublished, has been furnished with the greatest generosity by my colleagues of the International Health Division of the Rockefeller Foundation, Drs. Balfour, Barber, Rice, and Shannon in Greece, Collins in Bulgaria, and Hill in Spain. I have drawn freely on Professor Swellengrebel's reports; and to Professor Martini of the Hamburg Tropical Institute, a close collaborator for over three years, I owe not only a wealth of accurate observation but also authoritative counsel and stimulating advice. These gentlemen, however, have no share of responsibility in any but the soundest of the views hereafter to be expressed.

On the whole, the book is an outgrowth of the work of the Malaria Experiment Station in Rome, which exists no longer but has become, under Professor Missiroli's direction, the Laboratory for Malaria Studies of the new Institute of Public Health. To Professor Missiroli I stand in a special relationship. We have collaborated for such a long time that I hardly know which are his ideas and which are my own.

L. W. H.

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1936.

INTRODUCTION

NOT far from Rome, on the edge of the Pontine Marshes, stand the well-known and suggestive ruins of the medieval town of Ninfa, abandoned by its inhabitants for some good reason about the year 1640. The malariologists point to it (I almost said with pride) as one of the rare examples of the power of malaria finally to wear down human resistance. But the historians rather disconcertingly make use of the same episode to illustrate the destructive effects of the acquisitiveness of the great landlords, aided by the insecurity and general disorder of an age of belated feudalism. They imply that malaria was not the prime cause of the exodus or even perhaps an independent phenomenon, but was itself a product in large measure of the unsettled conditions of the times.

The advocates of the malaria theory point out that, although political and economic conditions have completely changed in the last 300 years, Ninfa and in fact the whole fertile plain of the Pontine Marshes has remained until now desolate and uninhabited for no other reason than the presence of the anopheline mosquito. We may as well admit that this argument is not as sound as it seems. Malaria by itself has rarely been known to dislodge a long-established agricultural community like Ninfa, entrenched upon such fertile soil. It is a tolerant and self-perpetuating parasitism which aims to enslave rather than destroy the populations which succumb to it. The victims ordinarily come to some sort of terms with their inveterate enemy, making an annual sacrifice of their youth to obtain for the old a certain tolerable freedom from attack. Something like this may be the meaning of that mythical tribute which Athens once paid in youths and maidens to the Minotaur until Theseus, forerunner of Gorgas and Ross, put a stop to the shameful situation by eradicating the cause.

But while malaria fails as a rule to overcome the tenacious resistance of an established community, it is very successful in preventing the reoccupation of land which has once been abandoned. Like a forest which has been utterly destroyed, a community under such conditions cannot naturally replace itself. The Volscians, we are told, once flourished in the region now called the Pontine Marshes, but after their cities were destroyed by the Romans the land remained uninhabitable for over 2,000 years, and all attempts to establish bodies of people upon it were tragic failures. The Tuscan Maremma, and indeed the whole coast of Italy from Rome to Pisa, was once thickly populated, but first the Goths and later the Saracens, and finally the armies of Pisa and Siena laid waste country-side and town and left malaria in possession. The barbarians, the infidels, and the land barons have long been dust, but the land has remained a desert till our day. The Romans and their successors the Italians, who were always great colonizers, could not colonize the little circle of cultivable land which lay immediately round their capital city. Celli quotes Machiavelli as writing, 'Unhealthy regions become healthy if they are occupied all at once by a large number of people.' He was mistaken. To colonize such regions successfully entails, as we know from bitter experience, a preliminary expenditure so great as to make the cost seem prohibitive.

We may assume then that feudalism and malaria *collaborated* to expel the citizens of Ninfa. The way they worked together is obvious. Lack of security in the tenure of land and the incessant warfare between the barons were disastrous to the development of agriculture. Instability of the peasants on the land favoured malaria, and malaria increased that instability. It is characteristic of malaria to exploit troubled situations and help round out vicious circles.

The feudal system, of course, did not lie at the bottom of malaria, for feudalism has passed away and malaria is still

with us. One aspect of feudalism, however, has survived, and this is the tendency of the ownership of vast tracts of land to become concentrated in the hands of a few individuals. These huge landed estates, known as *latifundia*, were almost invariably given over by their absentee owners to simple pasturage, interrupted by short intervals of extensive cultivation. The few inhabitants with their flocks and herds were migratory. There were no houses, roads, or water-supply. In fact, quite apart from malaria, the colonization of such areas was economically impossible to the owners. But far from diminishing, these great properties tended always to increase. Celli[1] states that from 1690 to 1871 the number of landowners of the Roman Campagna fell from 443 to 204, which means that the estates were constantly extending. Thousands of acres of good land, withdrawn from ordinary cultivation and highly malarious, supported only water-buffalo, horses, cattle, and sheep, which offered the greatest possible return on the small sums invested and the labour employed.

The conviction grew that it was the *latifundium* with its unhappy consequences that was responsible for the malaria. Crispi himself held that the only way to get rid of malaria was to break up the *latifundia*, and he would not listen when Celli told him that it was not the *latifundia* which maintained malaria, but malaria which had created and maintained the *latifundia*. In fact, if malaria prevents the farmer from living on his land, he cannot develop it properly and his smallholding becomes unprofitable. He is forced to sell it eventually to the great landlord, to the satisfaction of the local government, which foresees the possibility at last of being able to collect the taxes on it. But the land reverting to its natural state forms marshes, which breed mosquitoes and increase the malaria, thus starting the disastrous cycle anew. On the other hand there is much to be said for Crispi's view that the *latifundia* derive from long-established

[1] *The History of Malaria in the Roman Campagna* (London, 1933).

social and economic forces independent of malaria, which is merely a mischievous intriguer intervening to turn the situation to its own profit. Malaria, long rooted in the Balkan States, has not in fact resulted there in the establishment of *latifundia*. We are plainly dealing with one of those common binary systems in which, if either factor is taken as the cause, the other seems quite logically to be the effect. Thus Celli says that in 1881 there were 231 ruined and abandoned hamlets in the Roman Campagna, and he contrives to leave us in doubt as to whether this is to be charged to malaria, to the extension of the *latifundia*, or to both.

But while absentee landlordism and great undeveloped properties are characteristic of those regions where malaria is still intense, a little wider view of the problem makes it quite clear that we shall not find here the great underlying cause or mainspring (if there is one) which has kept malaria going through the centuries in Europe. Sardinia, for example, is much more intensely malarious than Sicily, yet it has been said that one-third of Sicily belongs to seventy-seven persons, while in Sardinia, as in India, upon the death of the owner the land has always been divided among his heirs, and in course of time has come to consist almost entirely of minute holdings, a good proportion of which are not large enough to support a family. Rossi,[1] director of the well-known Agrarian Institute at Naples, has pointed out that Sardinia is, however, the least cultivated part of Italy, as it is the most malarious. It lives on its pasturage and natural products. At best there is a primitive form of agriculture, which consists in an occasional sowing alternating with long fallow periods during which the soil recovers in part its fertility. He asks whether we have paid enough attention to the agricultural factor in malaria. It is a saying in Italy that malaria flees before the plough. In

[1] 'Tecnica e igiene delle trasformazioni fondiarie—Malaria, agricoltura e terreno agrario' (Lecture, Sup. School of Malariol., Rome, 1927).

fact, it is the unproductive south of Italy which is malarious, while in the highly cultivated north the infection no longer spreads, in spite of the anopheline mosquitoes which certainly show no tendency to disappear.

Nevertheless, the longer we study this question the more perplexing it becomes. There are, it is true, wide and prosperous regions where malaria and a highly developed agriculture seem to be mutually incompatible. In many of these places, as in parts of Holland and in the valley of the Po, it would not be practicable, with any of the methods at our disposal, to stop the breeding of anopheles mosquitoes. We can hardly escape the conviction that some social or biological force linked with agriculture is constantly at work to suppress the transmission of the infection. Then we remember at once that in other places, perhaps not far away, malaria persists in its severest forms in the face of an intensive cultivation of the soil, and indeed of a relative prosperity, as though it were not influenced in any way by these factors. Tropical experience shows that it is possible, with proper organization, sufficient funds, and a competent sanitary service, to establish and maintain a profitable agriculture in the most malarious localities, but only at the cost of perpetual and expensive warfare on the causes of the disease. There has never been any indication that malaria will spontaneously die out under such circumstances. The same thing is true of many regions of southern Europe, and repeated failures to put them under cultivation appear to have been due to an over-confidence in the social factors which elsewhere seemed so adequate, and to the neglect of specific measures of prevention which previous experience had dismissed as superfluous. The failures were usually ascribed to some other reason, and until very recently the paradox has not been clearly recognized that there are places where the intensification of agriculture has been followed by the disappearance of malaria, and there are other places, under parallel conditions and with the same species

of anopheline mosquito, where malaria has obstinately prevented the introduction or the intensification of agriculture.

I have dwelt at some length on the ambiguous role which malaria has played through the ages, appearing now as the cause and now as the effect of some social system or phenomenon, because this is really at the bottom of a serious division among malariologists of the present time. There are those who believe that malaria—or at least the malaria of temperate climates—is a social disease; that we must look for the causes of its persistence in Europe to underlying political, economic, or other social factors which favour its spread; and that, if these are modified or corrected, malaria will disappear of itself as an important health problem. There are others who can see malaria only as a local question—a parasitism adapting itself to all sorts of conditions, an opportunist able to turn social factors to its use but not dependent on them, and eradicable, in the last analysis, only through the effective abatement of its insect carrier. A satisfactory reconciliation of these two points of view is fundamental, it seems to me, to the adoption of any sound and co-ordinated programme of malaria control.

I

A HOUSE DIVIDED

If the trumpet give an uncertain sound, who shall prepare himself to the battle? (1 Corinthians xiv. 8.)

MALARIA had reached a very low ebb in Europe in 1914, and seemed to be receding annually toward the south-east in a halting but fairly satisfactory way, except for a few annoying pockets where normal subsidence was being held up, it was vaguely suggested, by 'local conditions'. The consensus of opinion was that this disease, like typhus and plague, was an anachronism among advanced people in modern times and would soon cease to be of importance in the temperate zone. Then, very suddenly and unexpectedly, malaria took a hand in the World War. I say unexpectedly, for although such qualified prophets as Ross, Laveran, and Nocht had clearly explained what was bound to happen to the British, French, and German armies on the Macedonian front, every one (including the medical officers) received the warnings of these doctors with amused contempt, and thus ignorance and incredulity set the stage for disaster. All these armies were surprised by a common enemy whose strength had been gravely underrated. In the autumn of that dreadful year of 1916 the French could put no more than 20,000 men in the line out of a force at least six times that number, and General Sarrail had to report to Government that his army was immobilized in hospital.[1] The British[2] had at least 30,000 men down with malaria in 1916, 70,000 in 1917, and no one knows what might have happened in 1918 had they not repatriated 25,000 of the worst and most chronic cases. Even then over two million service days were lost that year on account of malaria, as

[1] Sergent, Ed. and Et., *Arch. Inst. Past. d'Algérie*, **10** (3): 317, Sept. 1932.

[2] Wenyon, C. M., 'Malaria in Macedonia. Part I', *Jl. Roy. Army Med. Corps*, **37** (2): 172, Aug. 1921.

compared with a million the year before. The Germans derived no advantage from this predicament of their enemies; malaria, as usual, was exploiting a favourable situation to the utmost and had joined battle on both sides. We had the spectacle of three fine armies, backed by the most powerful nations of Europe and equipped regardless of expense with every modern appointment, virtually paralysed before they were able to strike a blow.

It was quite clear that in Europe there were still large areas into which outsiders could not venture with impunity. After the war was over, and in spite of its lessons, great mass interchanges of population in the Balkans and Near East kept heaping new fuel on the fire, until no one dreamed of being able to control it and nature was left to her own devices, while tens of thousands miserably perished. Soon malaria began to take the offensive. It dogged the footsteps of returning soldiers to their homes and infected countrysides whose inhabitants had never known the bitter taste of quinine. In Russia appeared the most terrible epidemic of modern times, comparable only to those of North India, and in Italy a recrudescence occurred in areas long free from the infection, with the loss of decades of patient and hard-won progress. Secondary cases began to appear in England, while in such an unlikely place as Emden on the north German coast there was an epidemic of 5,000 cases. Most remarkable of all, malaria appeared in the city of Archangel, and for the first time, as far as we know, the King of Tropical Diseases set foot within the Arctic circle. This was thoroughly bewildering. Stefansson had told us that inhabitants of the Arctic regions maintain in their houses in winter what amounts to tropical conditions. It was now rumoured that anopheline mosquitoes had adapted themselves to indoor life in the far north and were breeding in household water-containers. Even they had become infected by the wide dispersion of malaria carriers.

From remotest times war and malaria have always been

loyal allies. There began to be a fear of a great return to all parts of Europe of an endemic disease of the first magnitude which, like plague and cholera, had begun to lose its power to terrify a generation which had seen it in full retreat. A century ago malaria was like a great lake inundating all of Europe. Even before the middle of last century it was found to be gradually draining away by unknown channels, unaccountably subsiding to lower levels, abandoning first the cold north and then becoming shallow over great zones of Europe, finally revealing islands irregularly distributed here and there, but remaining in the deep pools which were the permanent centres of the more extensive endemic range of the disease. This silent, almost unnoted, withdrawal seemed to take place irrespective of the activities and efforts of man. The disease disappeared first in those places where little had been done to combat it, lingered still where the fight had raged most fiercely and where slight gains had been registered at great cost.

Apprehensions of a general rise of the endemic level were mainly unfounded. The great complex and organized exchange of gametocytes and sporozoites, which we call endemic malaria, was as unresponsive to human activities bent upon spreading the virus as widely and rapidly as possible, as it was to the previous activities attempting to restrain it. There were a few years—less than a decade—of unbalance. Epidemics of no great moment sprang up in unpredictable places and were explained very rationally by epidemiologists, and only in those deeper pools which had never dried up did malaria succeed in strengthening its hold on populations which had insecurely diked it out, or in overwhelming pitiable groups of unprotected refugees coming from healthy places. As a second deluge it was a failure, and as regards malaria Europe has already emerged to the point which it had reached in 1914, but it cannot be held that man has done much more than observe the process. One has the impression of a slow, spontaneous return to equilibrium

of a great natural mechanism thrown temporarily and slightly out of balance by a social convulsion which, on the political and economic level, has permanently affected the most deeply rooted institutions of mankind.

If we go back into history we realize that this must have occurred before, perhaps time after time, though never on such a grand scale: a disturbance more or less localized in human affairs, like a storm of limited extent but devastating character, leading to an associated disturbance of the intricate and age-old balance of man's environment, in which the factors favouring and those thwarting the exchange of malaria between anopheles and man had reached a precarious equilibrium. There would supervene a long wave of enhanced morbidity, gradually attenuating as the biological conditions rooted in secular adjustments returned to normal, and finally disappearing or perhaps persisting at a lower and more constant level in those areas where malaria transmission has always been permitted by nature. For the most part the reasons for these secular oscillations in the curve of malarial endemicity are inscrutable, because the internal adjustment of the elements composing a biological situation in dynamic balance is inconceivably complicated. As Martini says, a simple explanation of a natural phenomenon is probably wrong. Nevertheless, profound social upheaval attended by destruction, insecurity, prolonged disorder, and famine must be among the moving causes of the periodic subjection of man to malaria.

We know most about these periodic recrudescences and attenuations of malaria in Greece and Rome, where history is oldest and most precise. We must be careful to keep in mind that the early history of malaria is untrustworthy. Even in medieval England we cannot be sure, from the accounts that come down to us, what was malaria and what was not. 'Ague', in English, merely meant 'acute' and referred to any sort of fever, whether it was continued or remittent. Diagnosis in those days could not be specific in

the modern sense of the word, and was based on symptoms, not on aetiology. The over-simplification of clinical diagnosis could be amusingly illustrated in many a primitive population of much more recent times. Not long ago Professor W. G. Smillie, looking over old death certificates from the 'Eastern Shore' of Maryland, found that deaths unattended by a physician were ordinarily recorded as due either to 'inward' or to 'outward' hives, the latter referring to cases with some sort of eruption. If the throat were involved, a slight refinement in diagnosis was introduced by calling it 'thrash'. Unfortunates who could not be classified under any of these heads were certified as having 'perished to death'. I gather from Colonel James's researches that the term 'ague' was hardly more specific than 'hives'. So much less, then, can we penetrate the mysteries of the diseases of antiquity. Yet the studies of Celli and W. H. S. Jones[1] suggest the remarkable part which malaria must have played throughout the history of southern Europe. Hippocrates in the fifth century B.C. was acquainted with the swelling of the spleen among inhabitants of marshy regions. The cult of the Fever Goddess in Rome was extremely old; to Cicero it was already 'the *old* Fever Temple on the Palatine'. Cicero praises Romulus for having built Rome on a healthy spot in an infected region, and Terence in his *Hecyra* asks, 'What is it, fever? Quotidian?' Cato advises that enlarged spleens should be treated with cabbage. Virgil, in the third book of the *Aeneid*, says that settlement of the land was prevented by the summer disease. That Rome, twice mistress of the world, was a 'metropolis in the midst of a desert' can hardly be attributed to any other cause than malaria. For long periods the surrounding country was hospitable and offered the farmer health and prosperity; for long periods it turned hostile and implacable and reduced the work of man to ruin and desolation. The beginning of Christianity coincided with a period

[1] *Malaria and Greek History* (Univ. Press, Manchester, 1909).

of attenuation, but toward the close of the eighth century the tide began to turn. The barons were called from their castles in the hills to defend the plains from the Saracens' continual incursions, and ended by taking possession of the land themselves. Then followed the dark ages of military feudalism, the decay of agriculture, the insecurity of life and property, and the rising tide of malaria. The incessant raids of the Saracens, the invasion of the Huns and of the Normans, the everlasting wars between the nobles and their conflicts with the popes, kept all the land a solitude broken only by shepherds who, with their flocks, descended in winter from the mountains of the Abruzzi.

For centuries malaria was actually the protector of Rome. Foreign conquerors found it impossible to take possession of the capital of Christendom and make it their residence. The invaders were always decimated, but the natives were spared. Foreign popes and bishops died in rapid succession of malignant Roman fever during the eleventh and twelfth centuries. In the fourteenth century for a brief interregnum the Roman Campagna was again cultivated and well-populated and the Papacy returned to Rome, but in the sixteenth century malaria once more settled down upon the whole region and has prevented its development until the present time. Thus, in 1590, Sixtus V died of malaria fever after trips to the Pontine Marshes to supervise his drainage projects. A month later his successor, Urban VII, also died of malaria, caught at the Vatican itself during the long conclave that preceded his election. The most disastrous conclave of all was that of 1623, when eight cardinals as well as thirty secretaries died and a much larger number fell ill. Through the succeeding centuries malaria reigned undisturbed, and at the close of the nineteenth century Senator Garelli, one of the most enthusiastic advocates of colonization of the Roman Campagna, was compelled to report that land-reclamation in the Campagna had been abandoned and that he did not blame the Government for

coming to this decision. The efforts of Caesar and Augustus, of Sixtus V and Pius VI, of Napoleon himself and of all the engineers from the Risorgimento to the Great War, failed utterly to dislodge malaria from this little region lying round about a city which was, in many ways, the centre of the world; and, what is more remarkable, there is no evidence that Roman authority, technical skill, or financial resources in the slightest degree influenced the imperturbable rhythm of malarial comings and goings.

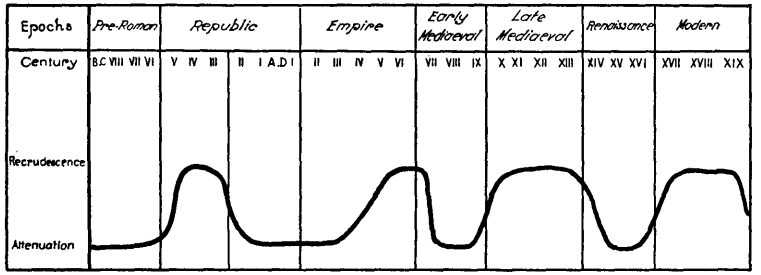


FIG. 2. MALARIA IN ITALY OVER THE CENTURIES (*after* Celli). The four great waves, occurring in periods of insecurity, and attended by a regression in agriculture and animal husbandry (Missiroli).

The major oscillations of malaria over the centuries seemed to Celli[1] autonomous, as though there were an inherent periodicity in the dreadful scourge. It appeared to him that when malaria entered upon one of its long attenuations, like a flood receding, agriculture sprang up and the people began with alacrity to occupy and cultivate the land and to become prosperous and forget the bad times. But when deliberately and almost unheeded the implacable enemy began once more to infiltrate the population, a blight would seem to descend upon the homes and the fields; all would slowly and inevitably fall to ruin, sullenly disintegrate and return to nothing at all. Sheep would graze in winter beside the crumbling houses, until with the lapse of cen-

[1] 'The vicissitudes of the history of the various civilizations and the various phases of abandonment of the Roman Campagna are to be attributed not so much to human events as to the periodical laws of the decline and recrudescence of malaria through the centuries.' Angelo Celli.

turies nothing remained to recall the happy epoch of a healthy and fruitful country-side.

We cannot now accept this fatalistic view of the great waves of malaria in the dark ages and medieval times. Celli's own picture of incessant social upheaval, of warlike barons and devastating invaders, confirms our observation that without peace and security an intensive husbandry will die and in its stead malaria will reign over barons and barbarians alike. Thus the recrudescence of endemic disease is rather the result than the cause of the decay of rural life and the abandonment of the land.

One thing has been established in recent times. Malaria has certain endemic homes in Europe in which it takes refuge during long periods unfavourable to its spread, ready to inundate large areas in the wake of war, famine, or even the upheaval consequent upon pioneering activities in undeveloped areas. In northern Europe these foci of malaria are not very many or of any great importance. The endemic covers much greater areas in the south, where it is more destructive and is a heavy incubus on the rural population. This is especially true of south-eastern Europe, where malaria becomes as universal and as severe as it is in the tropics. The distribution in its broad lines has not changed materially in historic times, and this, as we shall see later, is a very interesting and important fact. The intensity, on the other hand, while it has waxed and waned through the centuries, has without doubt been steadily diminishing for many years, rapidly in the north, more grudgingly below the Alps.

This seems quite logical and in strict accord with what we have always supposed to be the origin of malaria in Europe. It is *par excellence* a tropical disease, invading Europe, we are told, from Africa at an epoch which some students believe can be fairly closely approximated. It is an invader, like the Europeans themselves, into a relatively inhospitable clime to which man by intelligence and energy

has adapted himself, but where a parasitism, evolved and perfected in warmer temperatures and under more primitive conditions of society, has not been able to maintain itself everywhere with great success, and in very many places not at all. Certainly climate lays down the broad lines of malaria distribution, and the successive isotherms are increasingly difficult barriers to its successful advance from the equator toward the pole. Nevertheless, although this is a very simple and plausible explanation of the undoubted mitigation and retraction of the malaria endemic in northern Europe, even the early malariologists felt that there was something unsatisfactory about it.

In the first place, malaria has not so much receded as it has contracted, oftentimes toward the north rather than toward the south. Thus in Germany it is the northern coast which is still malarious, the south is free. In the second place, malaria is not one disease but is merely a convenient term which covers three distinct infections at least. Malignant tertian, called 'tropica' by the Germans, is certainly at home in the tropics. On the other hand, benign tertian seems especially adapted to temperate climates and to a winter pause in transmission, as we shall later see.[1] There is, therefore, no climatic reason why benign tertian should have abandoned south Germany or the French Riviera.

But what particularly puzzled Celli and Grassi was another and still more curious fact. There was no question in their minds, even in the early 1900's, that malaria depended upon mosquitoes for its dissemination. But they noticed that frequently in Italy the quantity of anophelines was not in direct proportion to the intensity of the endemic. 'In fact', wrote Celli,[2] 'it is oftentimes in *inverse proportion*.' This inconsistency was soon shown to be true not only in

[1] These old terms for malaria, such as malignant tertian, estivo-autumnal, benign tertian, &c., are local in origin and restricted in use, and should be quietly abandoned in favour of a more exact terminology based on the organism, as *falciparum* and *vivax* infections.

[2] *La Malaria* (Turin, 1910).

Italy but for the rest of Europe as well. The first report of the Malaria Commission of the League of Nations,[1] on its international investigations in 1924, dwelt on the fact that there was a complete absence of correlation between the evidences of intense malaria and the relatively few anophelines found in houses in parts of southern Europe. It was deduced that a small number of anophelines can keep up a high degree of malaria transmission. But if the threshold of anopheline density seemed so low in certain places, it turned out to be disproportionately high in others. It is easy in Europe to find localities with incredible numbers of anophelines—tens of thousands in a single stable—and with no malaria whatever. 'The geographical distribution of anopheles', said Celli, 'cannot be made to coincide with the map of malaria.'

It comes as something of a surprise to those not actually engaged in malaria epidemiology to learn that there are anophelines everywhere in Europe but that malaria is curiously restricted, for no evident reason, to certain localities. In the general absence of malaria, no one except systematic entomologists had paid much attention to the anophelines. They were not insects apparently which bothered people to any great extent, for Ross[2] says that Theobald did not think they bit man in Britain, and Roubaud[3] says the same of Meigen, who was the first to describe *A. maculipennis*, the principal malaria carrier of Europe. Over a large part of Europe they were insects of no medical importance to man or beast, and it seems to have been taken for granted that they had withdrawn along with the malaria. They were certainly not pestiferous mosquitoes, and only when Roubaud and Wesenberg-Lund, shortly after the War, discovered them blackening the walls of the stables of France and Denmark, was the fact appreciated that the anopheline population had remained in undiminished numbers while malaria had incomprehensibly disappeared. Roubaud[1] and Wesenberg-Lund[2] had uncovered the fact that there was a problem of *anophelism without malaria.*

[1] *L.o.N. Hlth. Org. C.H./Mal.*/68–72, Geneva, 10 July 1924.
[2] *The Prevention of Malaria*, ch. 5, p. 214 (London, 1910).
[3] *Ann. Inst. Pasteur*, **32** (9): 430, Sept. 1918.

This situation creates more than surprise—it creates a lively scepticism as to the fundamental validity of the thesis that malaria can actually be controlled by reducing the numbers of anopheline mosquitoes. An influential article by James[3] in 1929 discussed the causes of the disappearance of malaria from England. 'In a number of districts in which malaria did not spread', he wrote, 'the prevalence of anophelines was greater than in the endemic areas. . . . In fact, it was seldom or never possible anywhere to correlate the numerical abundance of anopheles with the amount of malaria. . . . It is surprising that a section of the older school of malariologists still pin their faith to "anopheles reduction" as the best method of controlling malaria.' Certainly it did not seem like common sense to struggle toward an imperfect restriction of mosquito breeding if their numbers had so little to do with the intensity of malaria.

Celli called attention to another inconsistency between the popular idea of malaria and the actual situation in Italy. If there were swamps without malaria, there was a great deal of malaria without swamps. The name *paludism*, therefore, was as much a misnomer as *malaria*, a word introduced anonymously into the language in 1793. In fact, the major part of the hyperendemic malaria in Italy occurs in exceptionally dry hilly zones of the south and the islands (Sardinia and Sicily). 'In the south', adds Celli, 'the marshy regions constitute a small fraction of the total area dominated by malaria.' In contrast to this situation, many of the great marshes of north Italy and north Europe were not associated with any malaria at all.

[1] *Ann. Inst. Pasteur*, **34** (4): 181, Apr. 1920.
[2] *C.R.Soc. de Biol.* **75** (21): 383 and 386, 16 July 1921.
[3] *Proc. Roy. Soc. Med.* (*Sec. Epid.*), **23**: 71, 1929.

There is besides a further complication in the matter of the seasonal distribution of malaria. In spite of the fact that the anophelines do not come out of their winter quarters in Holland and Germany until June, it happens in certain places, and perhaps rather generally, that the bulk of the malaria cases appear in April and May, and no connexion can possibly be discovered between the two phenomena. What Korteweg[1] and Martini[2] observed in Holland and Germany, others have noted in widely separated parts of Europe. Thus James writes for England, 'The seasonal incidence of clinical malaria differs for each species of parasite and cannot be correlated with the seasonal incidence of the infection in anopheles mosquitoes.' Clinical malaria in the spring, malaria in the mosquitoes in autumn and winter, is characteristic also of Russia and the Scandinavian countries, and has been noted as far south as Spain.

The distribution of malaria, therefore, seems quite capricious both in time and in place, and its intensity appears often to be independent of that of anopheline production. Apparently this is not true in any part of the tropics, and, although this accumulation of inconsistencies did not succeed in throwing doubt on the mosquito theory, it introduced a new unknown. This was perhaps the baffling element which Grassi[3] called 'factor *x*', introduced into the simple equation *man*+*anopheles* = *malaria*. It seemed to make any attack on the mosquito, short of complete eradication, almost absurd as a method of reducing the amount of malaria. What was needed, every one said, was more knowledge before continuing to spend public funds in ways which might prove uneconomical because ineffectual.

It is true that success had been reported from various parts of the world, and principally from America, in the

[1] *Herinneringsbundel v. Prof. Rosenstein*, p. 263 (Leiden, 1902).

[2] *Berechnungen und Beobachtungen zur Epidemiologie und Bekämpfung der Malaria*, p. 14 (Hamburg, 1921).

[3] *Prima relazione sull'esperimento a Fiumicino* (*Roma*), Min. dell'Int. Dir. Gen. della San. Pubb. (p. 52), 1919.

application of mosquito-control measures. Panama was incontestibly a success, but in the tropics work is practically never carried to the point of complete extinction of malaria. The tropics are inundated to a great depth with chronic malaria, which can be drained away only to a certain level, comparable perhaps to that of western Europe at the present time. Possibly at this point the correlations begin to fail and the 'factor *x*' to appear.

Dr. Wolter[1] of Hamburg, and many others as well, who have consciously or unconsciously remained in the Pettenkofer school, have never abandoned the belief in an environmental factor linked with the soil and more particularly with the water table, which is subject to vertical oscillations over long periods. The great Russian epidemic of malaria in 1923, and its association with other diseases, is an example of what they attribute to *Klima und Boden*. In Panama, according to this hypothesis, the French were unlucky enough to hit upon years favourable to epidemics, while the Americans took over at the beginning of a period of rapid natural decline in mosquito-born diseases. This alone enabled them to complete the Canal, although, as often happens, the sanitarians, who had been prodigiously active all the while and had spent a great deal of money, took to themselves all the credit for success.

Such a conception finds little credit nowadays, but among the older engineers at the present time it is not rare to find a very firmly rooted feeling, even if we cannot call it a theory, that the condition and disturbance of the soil is intimately linked with the successful transmission and persistence of malaria, not explainable in terms merely of mosquito numbers and their contact with man.[2] Thus the work of pioneers in previously uninhabited areas, and the

[1] *Die Malaria in Russland* (Munich, 1930).

[2] Bellincioni considers that rainfall affects malaria intensity, not only through anopheline production, but also through the level of the subsoil waters, which shows a parallelism with the epidemic curve of malaria at Grosseto. (*Riv. Malariol.* **13** (2): 201, 1934.)

reclamation of inundated land will seem to create malaria where it did not exist, and often raise its intensity to extraordinary heights until, with the return of stable conditions, the malaria will finally depart of its own accord, in spite of the continued presence of the malaria mosquitoes against which no measures whatever have been taken. 'Nothing but the greatest wilderness', wrote Aschenfeldt in 1845, 'or the most perfect cultivation protects an area from malaria fever.'

Out of such experience has arisen the doctrine that the elusive factor, Grassi's *genius loci*, which in the end determines whether malaria shall persist or disappear in a locality, is in some way connected with agriculture. It is easy to say, 'Malaria flees before the plough', but if true this only intensifies the mystery. It turns out that cultivation need not in itself entail the drainage of the land and consequent reduction of anopheles breeding-places. The great rice-fields of Vercelli in north Italy, and Valencia in Spain, continue to produce their milliards of *Anopheles maculipennis*, the notorious vector of malaria in Europe; but of malaria there remains hardly a trace to-day, intense as it was during the pioneering and reclamation period.

Marchoux[1] has called attention to the extraordinary scheme of crop rotation in La Dombes, in central France. In this rolling country, low places can be inundated and drained easily at will, and so fish-culture alternates with agriculture on the land. Three years under water with a dense algal growth and many fish render the rather poor soil capable of producing a good crop the following season. There are literally millions of anophelines but no malaria. On the other hand the most costly schemes of drainage in other areas, combined with the most generous and assiduous medical care, have often come to failure in the end. Malaria resists all pressure and inducement to depart, and eventually ruins the enterprise. Thus Celli was forced to report in 1902 that, in spite of the great land-reclamation works on

[1] *L.o.N. Hlth. Org. C.H./Mal./*78, Geneva, 28 Feb. 1927.

the Tiber delta near Ostia begun in 1885 and terminated in 1889, comprising a network of efficient drainage canals and ditches leading to central pumps which lifted the water into the sea, malaria after fifteen years had not shown the slightest tendency to diminish. It still rendered the fertile area, so near the great markets of Rome, unproductive and almost uninhabitable. And this was all the more tragic because the eager and industrious farmers introduced from north Italy perished miserably, although, in their own flat northern country in the valley of the Po, the same sort of drainage by open canals and hydrovores had permitted the establishment of prosperous and healthy populations on previously inundated land. In the one area malaria had found itself unable to maintain its millennial foothold; in the other it paid not the slightest attention to the most strenuous efforts of man to dislodge it, though the methods used were precisely the same.

It is, therefore, no wonder that uneasy doubts, ripening into frank scepticism, greeted the reception in Europe of reports from the New World that malaria was a simple function of anopheline density and that the one is quickly responsive to changes in the other. The American thesis, if we may call it so, seemed entirely too simple. As a matter of fact, the antilarval methods proposed by the Americans did not seem to work very well outside the United States. Panama was not really a convincing demonstration, because of certain extraordinary features. The immense sums spent on the sanitation of the zone ten by forty miles in area did not have to be raised by taxation of the local population, but came in virtually unlimited quantities from an outside source, bent under any circumstances on making a success of the Canal. The financial resources of the people and the economic value to them of protection from malaria was not taken into consideration. In Puerto Rico, and especially in the Philippines, the war on malaria did not seem to be making any greater progress than it did in other parts of the

world. In the latter archipelago the permanent base of the military force had been removed to the hills, and even there it was difficult to protect the soldiers, who had an excessively high malarial-sickness rate.

It was only natural for the League of Nations Malaria Commission to send a delegation to the United States to examine the malaria situation, its amelioration in recent times, and the causes of this amelioration. Two very experienced and competent malariologists were sent in 1927 and returned to Europe with a report which caused a great deal of discussion and some vivacious criticism from protagonists of this or that method of artificial, as opposed to natural, malaria control. The report said in substance that malaria was decreasing at a constant rate from north to south in the United States, a course which had begun, like that of other social diseases, before active measures had been taken against it. The Committee thought there was very little endemic malaria in the United States to start with, and that it was gradually dying out for reasons connected rather with social and economic progress than in consequence of preventive activities of health organizations. This irritated those Americans who thought justice had not been done to great and costly accomplishments in draining and protection, and the report was merely circulated in mimeographed form and not officially published to the world. But informed and intelligent opinion in Europe began to crystallize in opposition to spending large sums of public money in what seemed futile attacks on the anopheles mosquito which, even if reasonably successful, might for unknown reasons not have a proportionate effect on malaria incidence.

It is perhaps characteristic of Anglo-Saxon mentality to pay insufficient attention to the illogical nature of a project and to attempt to put it to the proof in the face of its theoretical impossibilities. The Rockefeller Foundation had established, in collaboration with the Italian Health Department, the Malaria Experiment Station in Rome, the first of a series of laboratories for field studies and experiments in malaria control now distributed in the various Mediterranean countries. It was decided to select a very malarious village and to attempt to control the malaria by anopheles reduction. To forestall criticism, the budget was fixed at the sum of money which the inhabitants had spent the year before on treatment of malaria. It was the first experiment in Europe with the new larvicide Paris green, which was, within a few years, to displace the spreading of oil upon the waters. With this new weapon anopheline breeding in and about the town of Portotorres (Sardinia) was cut down to a minimum, though not actually stopped, and the malaria began rapidly to disappear from the population (Fig. 3).[1]

It was discovered that one could never quite get rid of the anophelines in the town because of their powers of flight. In the tropics the elimination of breeding for half a mile around the locality to be protected had proved to be sufficient, and in America a mile. It appeared that at Portotorres the work had to be carried out to between two and three miles of the town to reduce the numbers to what was considered a safe maximum. This in part explains the failure of some of the antilarval experiments which had been undertaken in Europe, only to be abandoned for lack of results.

More important, however, was the discovery of the essential reason for the failure of the classical methods of larva control to accomplish in Europe what they had succeeded in doing in America. The European *maculipennis* is a very near relative of the American *quadrimaculatus* and resembles it closely, but it has an advantage over its American cousin, for it can breed in the edges of flowing water, while the other is a pool breeder. Thus the slow-moving perennial rivers of Sardinia and Sicily, which are the principal sources of anophelism and of malaria in those regions,

[1] Hackett, L. W., *Trans. Roy. Soc. Trop. Med. & Hyg.* **22** (6): 477, Apr. 1929.

would be completely innocuous in America and would not be taken into consideration in the application of antilarval measures in any part of the United States where *quadrimaculatus* is the vector. If you put water into motion in America you greatly reduce the breeding of the principal

PORTOTORRES (SARDINIA) 1924-1933
RESULTS OF 10 YEARS OF ANTILARVAL MEASURES

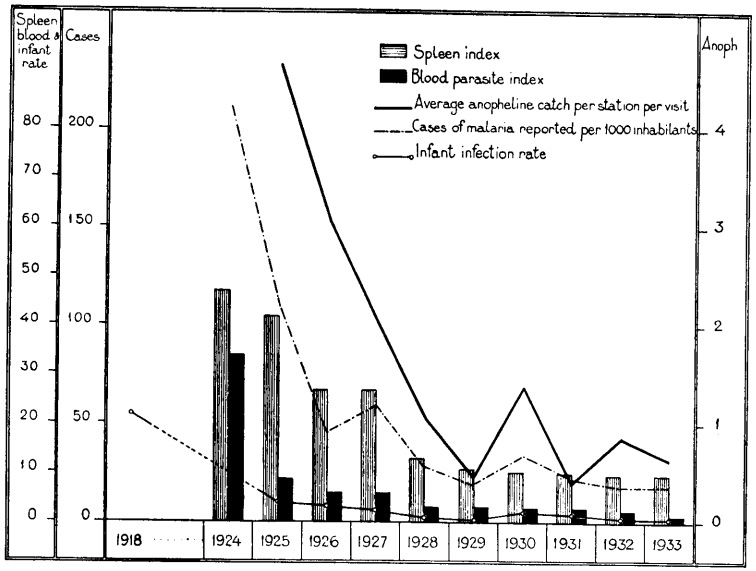


FIG. 3.

malaria vector, and hence no attention need be given in practice to streams and rivers and drainage systems with sufficient flow. In Italy the failure of the reclamation project of the Tiber delta was due to the fact that the network of canals provided the anophelines with more favourable conditions for breeding than the swamps which they replaced. As Grassi remarked, the irregular marsh had been transformed into a rectilinear one, and the breeding continued in greater measure than before. Oil was ineffective under such circumstances, but the discovery of Paris green saved the situation.

The success in the little Sardinian village of Portotorres made a great impression locally. It had been the practice to send a certain number of malarious children to the mountains each summer, and the cost of maintaining a child in one of these camps for seven months was about 2,000 lire. It now appeared that for the expense of sending twelve chronic cases out of Portotorres annually, the town had been made safe for every one of its 1,500 children and their parents. To rival the mountain colony we had established a sea-side resort, and the result was that in a few years children began to be sent to Portotorres—a welcome contrast to its previous notoriety as a place to avoid between June and September. Portotorres, however, although it was written up and was visited by many famous malariologists in person, failed to convince an incredulous Europe. The elimination of malaria from a three-kilometre circle in Sardinia made little impression on a world faced with a million deaths a year, and yet it was a very logical start in the field campaign against a disease characterized by the local nature of the factors which determine its endemicity. More Portotorreses began to multiply in Italy, but at the same time in Geneva the malariologists of the League, after a brief but rather thorough international survey of the malaria situation,[1] published a report in 1927, the keynote of which was restraint and caution. The report began: 'When the discovery of the mosquito cycle of the parasite was made it was almost universally believed that a single, simple method had been put within our grasp, capable of application in all malarious districts. Since then three decades have passed, and such a method is still to seek.' It appeared that no progress had been made in the twenty years since Celli wrote: 'The existence of swamps and of anophelism without malaria opens another lacuna in our epidemiological knowledge and suggests directives in malaria prevention entirely independent of the anopheline theory.'

[1] *L.o.N. Hlth. Org. C.H./Mal./73*, Geneva, July 1927.

Attention was sharply recalled to the primary duty of all antimalaria effort—the treatment of the malarious sick. This had apparently been neglected in some places in the wave of enthusiasm aroused by Barber's discovery of the effectiveness of Paris green in reducing anopheline breeding. 'We have seen some extreme instances', ran the report, 'in which so much of the time of the available medical men was taken up by antilarval measures in the field that little or no treatment of the people who were ill in their homes could be carried out.' The direct attack on the plasmodium in the human host must be maintained and brought above the standard called 'minimal effective degree of perfection', and to this the Commission added another measure, not so new as it was untried in any co-ordinated and intensive way: the direct attack on the plasmodium in the insect through the co-operation of the people themselves in killing anophelines found gorged with blood in bedrooms. The Commission had great confidence that this method would yield startling results if it could be carried out with persistence and thoroughness. This was to be the first line of attack. In the second line were all the so-called indirect methods aimed at protecting the human being from the bites of mosquitoes. The report was a disappointment to the majority of public health men actually engaged in antimalaria work in the field. Both measures recommended by the Commission, even if their proper application held out any probability of success, which many doubted, required the active and daily collaboration of the malaria-ridden inhabitants themselves, a resource upon which health officers have come to place no reliance whatever except in populations under rigid discipline, or obsessed by the terror of an unknown danger.

Certainly the appeal to quininization could not be expected to arouse much enthusiasm. It was a time-honoured resource with a history of three hundred years of constant defeat, always eagerly abandoned in favour of anything new

and promising, wearily taken up again as the irreducible minimum of all relief work in malaria. After all, medical assistance to a population in the clutches of a great endemic disease affecting principally the poor is a fundamental duty of the State. This has never been denied, I think, by any malariologist of whatever school. The confusion and opposition have arisen from the complacent practice of health authorities in regarding treatment as a preventive measure, and in considering that their duty toward society with respect to this disease has been discharged by making quinine easily and cheaply accessible to the people.

From what I have said it will be seen that the reduction of mosquitoes through larva control, and the reduction of plasmodia by treatment, did not either of them have a favourable press in 1928. Each had its defenders, sincere in their faith and enthusiastic over significant successes, but the assembled malariologists at Geneva found it difficult to believe that any considerable inroad had been made on either the anopheles population of the world or the plasmodial population of its inhabitants in the decade since the Great War. In spite of the successes, malaria was undoubtedly more widespread and more intense than in 1914. The condition of the world was very much like that of the chronic invalid in De Morgan's novel, who was always a little better than yesterday and never quite so well as last week.

A third group was rather rapidly forming at the expense of the other two. This was the school of those who did not believe in either of these methods, or in fact that we had any effective recourse against malaria at all. Symbolic of this feeling of complete pessimism was the laconic answer of the old man in one of our Italian stations who, when asked when he had had his last attack, replied, 'Not yet.' It was reflected in the Second Report of the Malaria Commission which said, 'The history of special antimalaria campaigns is

chiefly a record of exaggerated expectations followed sooner or later by disappointment and abandonment of the work. This record of failure and disappointed hopes makes it clear that the only prospect of real progress lies in renewed activity in the continuous study of the disease in all its aspects.'

An acknowledgement of ignorance is always an incentive to research. It was perhaps natural that those responsible for fundamental discoveries in the transmission of malaria should have pressed for action and have deplored the time and money spent in further study of the minutiae of a problem already solved. But under close examination malaria became only more intricate and impenetrable, more protean in its character, more diverse in its local manifestations. The growth of agnosticism as to its effective control was perhaps a good sign. As Jowett once remarked, '*Agnostic* is only a Greek word the Latin for which is *ignoramus*.'

One unfortunate result of the partial knowledge which had been gained by superficial study of the spontaneous disappearance of malaria was the feeling that, if we could only find it, there must be some easier way to deal with the disease than any of those laborious methods with which we have been struggling for a quarter of a century—some biological miracle which might banish it by the waving of a wand. Such an attitude is often paralysing to present action and may be made a plausible excuse for abandoning hard and unremitting labour. Certainly the lot of the malariologist at present—at least of such as belong to the 'old school', who persist in wading in swamps, creeping under beds, and sweating under August suns to outwit the persistent and innumerable anopheline—is not a happy one. I remember with a feeling of appreciation the comment of a small Moslem Albanian boy, in whose miserable and infested home I was conscientiously crawling about to find every mosquito. 'Even if I were a Christian', said the small boy gravely to my assistant, 'I wouldn't do

that.' To every worker there come moments when the incubus of malaria appears as immovable and permanently planted as the ice cap of a glacial period, and our petty efforts to destroy it as inadequate and disproportionate as an attack on a glacier with pick and shovel. Yet we cannot doubt that its hold is none the less precarious in the balance of nature, and that an insignificant but persistent environmental change might suffice to melt it all away. This, in fact, has evidently taken place spontaneously in parts of Europe within the memory of man. Time, after all, is really of no consequence. It has been every one's dream that he might set some mechanism in motion which, through the enlistment of natural causes, would eventually lift the burden of malaria.

We are not waiting idly for such a discovery. The failures of the past, the problems and mysteries of present-day malaria in Europe, the dream of a better way around the corner, have led after years of stagnation to a period of research in laboratory and field as intense and productive as that which followed the original discoveries of Ross and Grassi, Golgi and MacCallum. This has followed two different paths. The clinicians and their allies, the biological chemists, have sought a drug which will accomplish what quinine cannot do, namely, destroy those stages of the malarial organism which infect man and mosquito and which cause relapse. On the other hand, the epidemiologists and their allies, the entomologists, have attacked the problems and mysteries of malaria endemicity and distribution, trying to make sense out of a seemingly inchoate situation. Both have had remarkable success. A mine has been reopened after a long period and found to contain as much gold as was ever removed from it in the great days of the first discoveries. New methods have opened the way to veins of the richest ore, hidden to the early workers.

It is these discoveries which I shall now endeavour to lay before you, emphasizing their practical import in the

prevention of malaria. We have not yet discovered the *therapia magna*, nor can we by pressing a button liberate forces at a distance which will spell the extinction of endemic malaria over great areas. But we have the power of an increasing knowledge and the courage gained by partial successes in numberless small fields which, in their entirety, compose the whole problem of malaria.

Let us follow the trail of the epidemiologist, leaving the preventive therapeutics of malaria for subsequent consideration.

II

THE MALARIA PUZZLE IN EUROPE

By experience we find out a short way by a long wandering.
ROGER ASCHAM

THE natural starting-point for field research in 1925 was an examination of the unknown cause or combination of circumstances which had led to the spontaneous disappearance of malaria over large areas in Europe. The world was not without theories to explain this. Practically every one interested in the malaria problem of Europe had an opinion on the subject with another in reserve. Swellengrebel remarked that such was the fascination of this mystery that health officers became entomologists and forgot preventive medicine. Malariologists were becoming more interested in the anopheles which did not transmit malaria than in those that did.

There seemed to be no possible explanation which had not been proposed and supported by some authoritative person. This, after all, is the approved method of epidemiology. There are at first a great number of purely intellectual hypotheses which seem to fit a certain proportion of the observed facts. There is later some one who discovers the truth with methodical labour or brilliant insight, and at the end there are two claimants for honour, the one who happened on the correct hypothesis and the one who proved it true—the early philosopher who guessed the earth to be round, and Columbus. Most tentative hypotheses are of necessity wrong. What Pearl said of crucial experiments, that those which have been most loudly hailed at the time they were made have been subsequently found to lead to quite erroneous conclusions, is equally true of epidemiological deductions. The present problem presents an excellent example of this truism.

In view of the presence of anophelines in great numbers in immune areas, it seemed quite likely that they had become incapable of transmitting malaria in certain places. It was Alessandrini's[1] theory that they had become resistant to infection. In a study of the rice-fields of northern Italy he observed such an extraordinary production of large *maculipennis* females that he argued that the unusually favourable breeding conditions had produced a race of robust mosquitoes unsusceptible to plasmodial infection. Although Alessandrini carefully avoided the dangerous *experimentum crucis*, this had already been performed by Grassi, who had easily infected the anopheles from the rice-fields of Tuscany. In fact, Grassi's[2] theory of robust mosquitoes was precisely the opposite of Alessandrini's. The men of the Middle Ages considered that it was dangerous to allow the salt water of the sea to mingle with the fresh water of the coastal marshes, since they observed that the salty areas were always extremely malarious. Grassi sought to justify this medieval conception by showing that brackish water breeds robust anophelines which easily become infected, live long, and are therefore the most dangerous.

D'Hérelle's[3] observations on the Nile delta led him to associate the innocuousness of the anopheles with the cultivation of a certain type of clover, *Melilotus altissima*. He thought there was an active principle in the clover honey which either kills sporozoites in the mosquito glands or protects the anopheles from infection. This theory got into the popular magazines and inquiries, were instigated in various parts of the world where this clover was found. The public fancy was struck by the rather odd idea that perhaps the mosquitoes were being more efficiently treated

[1] 'La risicoltura e la malaria nelle zone risicole d'Italia', *Min. dell'Int. e Econom. Naz.*, Roma, 1925.

[2] *Atti R. Accad. Naz. Lincei*, Ser. 2, **31** (12): 535, 17 Dec. 1922.

[3] *Immunity in Natural Infectious Diseases* (Baltimore, 1927), also *Am. Jl. Hyg.* **16** (2): 609, 1932.

for malaria than the people. Soon, from Holland,[1] from the Argentine, from Corsica, came trustworthy reports that the distribution of clover seemed to have no relation to that of malaria, and in the laboratory Bruce Mayne[2] subjected large numbers of infected mosquitoes to varying treatments by *coumarin*, which is the active principle of the clover nectar, but without any success in curing the malaria.

Since the mosquito seemed everywhere to be ready and able to spread the infection, the possibility was entertained that man might, under certain conditions, be able to resist it. Barber[3] writes of the disappearance of malaria in the United States, 'It would seem *a priori* that where so great a fire has burned and gone out of itself, there must have been a lack of suitable fuel. It is plain', he adds, 'how closely the prevalence of malaria was associated with pioneer life and its decrease with the agricultural development of the country.' Now no such transformation has taken place in Europe in the last fifty years as that which has almost completely altered the tenor of rural life in America. Nevertheless, it was felt that proper treatment, combined with good food and a modicum of prosperity, has been within the reach of the European peasantry only in comparatively recent times, and that this might explain the southward trend of malaria in the Old World, as in the New. It is an old saying in Italy that *malaria vien' dalla pentola* (malaria depends on what comes out of the pot), and Cavour is said to have remarked that a good beef-steak is the best preventive of malaria. Colonel Gill[4] in considering the great epidemics of north India, often preceded by famine, says, 'The most important antimalaria measures may not be antilarval operations or even the systematic exhibition of quinine, valuable adjuncts though they may be, but the institution of measures to

[1] Swellengrebel, N. H., *L.o.N. Hlth. Org. C.H./Mal./51*, Geneva, 25 July 1925.

[2] *Ind. Jl. Med. Res.* **17** (3): 963, Jan. 1930.

[3] *U.S. Pub. Hlth. Repts.* **44** (43): 2575, 25 Oct. 1929.

[4] *The Genesis of Epidemics* (London, 1928).

ensure that the labour force is properly housed and more especially properly fed.'

The most enthusiastic and at the same time the most disastrous attempt to act on this theory was that of F. Cirio, an Italian fruit-canner, in 1897. He established an agricultural colony of Venetians on the broad and fertile but uninhabited acres of the Pontine Marshes. He used to say, '*Ma che malaria!* Malaria comes in through the kitchen. I am going to give them meat, wine and coffee and quantities of quinine.' Dr. Cardinali, the physician of Terracina, later wrote, 'It was enough to move one to tears to see those robust colonists come down from their mountains in the pink of health, only to fall stricken with the thunderbolt of pernicious malaria against which neither the generous living provided by Cirio, nor the quinine which I distributed with open hands, was any barrier.' Perhaps this was not a fair test, but in Europe, at least, as one surveys the field, it is not the people under economic strain who suffer the most from endemic malaria.

It seemed more probable that the factor which prevented the spread of malaria was in the environment rather than in any progressive change in man or in the mosquito. To return to Barber's simile, the fuel seemed still to be combustible and the lighted match always at hand, but something in the atmosphere prevented the fire from self-propagation. The simplest explanation lay just at hand. It was suggested by an Italian, Bonservizi[1], as early as 1903, that the attraction of well-stabled domestic animals had brought about a dissociation between man and the mosquito. Marchoux, in his recent observations on the diminution of malaria in the Dombes and Camargue districts in France, concludes that *A. maculipennis* is by nature a parasite of domestic animals. Where these are scarce or live in the open the anopheline has no other retreat except the house,

[1] *Corriere Sanit. Milano*, 25 Jan. 1903; quoted by Grassi in *Ann. d'Ig.* **32** (6): 431, June 1922.

where, in spite of its natural inclinations, it is forced to feed on human beings and thus becomes (rather abnormally) a malaria carrier. He believes that 'malaria disappears spontaneously in the face of agricultural development, regardless of persisting anophelines. This regression can be accelerated by sterilizing the carriers of the germs.' The relative attraction of houses and stables to the anopheline mosquito would thus determine its behaviour and, in consequence, the maintenance or disappearance of malaria.

Since stables are, in fact, exceedingly attractive to *maculipennis*, it would not seem at all improbable that these mosquitoes should tend to frequent places which offer a nightly food supply and which are dark, humid, warm, and relatively free from draughts. And if it is assumed that a certain combination of physical circumstances leads anophelines to remain in houses or return to them frequently, then the converse should also be true: namely, that the absence of these conditions will tend to keep them out. From this theory has sprung a whole programme of malaria prevention based on the improvement of housing, betterment of social conditions, and raising of standards of living which might permit us to relegate to second place, or even abandon, any effort for the suppression or reduction of anopheles breeding. In fact, James, after considering each factor which has been thought to have some influence on the disappearance of malaria from England, has come to the conclusion that 'the diminution of local malaria in England was due neither to natural causes nor to the intentional application of any particular preventive method reputed to be specific, but to progressive improvements of a social, economic, educational, medical, and public health character'. In other words, civilization itself has broken the association between man and anopheles. Like plague and cholera, malaria should disappear from communities with proper standards of living, and man can best accelerate the process by supporting general measures of social advancement.

Some observers have not failed to point out that this hypothesis is the best explanation we have of the slow but constant withdrawal of endemic malaria both in Europe and America from the north toward the more hospitable south; hospitable not solely in its climate, but also in its average lower level of prosperity and social advancement. They believe it is safe to state that during the last century increasing welfare and education, as well as a progressive application of science to living, have been developing gradually in the north, especially among the common people, while southern Europe has remained relatively backward, ignorant, and poor; and since poverty and ignorance are the secular allies of disease, it is not surprising that the malaria invader has been forced backward and compelled by an enlightened civilization to retreat towards the tropics, where social and economic conditions still permit it to feel at home. To this some Italian student might object that, after all, the Renaissance began in southern Europe and that culture and enlightenment spread northward rather than southward, and not too rapidly at that. In fact, from the earliest historic times, this has been the habitual orientation of European culture. But still the lot of the peasant farmer, the methods of agriculture, and the well-being of the great mass of the rural population were getting significantly better north of the Alps at the very time that malaria, once ubiquitous, was beginning to become focalized and to relinquish vast areas from its dominion. There seems very little mystery or even doubt about this, and it probably represents along general lines the opinion of northern peoples about the question of the present distribution and tendency toward regression of the malaria of Europe.

Nevertheless, there are a number of contradictions in this hypothesis which have aroused little attention at a period when malaria has ceased to occupy the minds of health departments, except as a problem of some tropical colony. One is the fact that the spots in which malaria lingers on

interminably as a mild endemic, undisturbed by all efforts to dislodge it, are far from being the most backward, poverty-stricken, and ignorant of northern Europe. North Holland, the east coast of England, and the northern coast of Germany suffer periodically from the disease, while Ireland, south Germany, and southern France are free. Malaria is actually correlated with high standards of living, agricultural advancement, and an unfavourable climate.

In contradistinction to these foci of endemic malaria in healthy territory, there are small and well-defined areas in the south which are malaria-free, though in the midst of highly malarious zones. Naples and the Nile delta are good examples. Why should malaria disappear permanently from the plain of Naples and the adjacent valley of the Sarno, located between two notoriously unhealthy regions to the north and south of them, or from the Ligurian coast or southern Tuscany (in close touch with the notorious Maremma), or in Jolanda di Savoia, a small central zone of the malarious Po delta—all islands surrounded by a sea of malaria—and still remain inextinguishable in Emden and around Amsterdam?

This is not to be accounted for by alleging the prosperity, intelligence, and industry of the people, since the farming population of North Holland and northern Germany is certainly not inferior in these respects to that of the rest of Europe. They are, in fact, if anything somewhat better off than their confrères in southern Holland and southern Germany. And it must be remembered that alongside of each malaria-free area, and serving as it were for comparison, is one in which malaria remains endemic, although inhabited, as far as one can judge, by the same sort of people under the same social and economic conditions.

In 1921 Roubaud[1] proposed a new theory for the spontaneous disappearance of malaria, based on competition among the anophelines for food. He observed that it is

[1] *Bull. Soc. Path. Exot.* **14** (9): 577, 9 Nov. 1921.

where the anopheles are being produced in the greatest numbers that malaria has tended first to become mild, then sporadic, and finally to disappear. He discovered that the number of teeth which an anopheline may have on its maxilla varies widely from individual to individual of the same species, and may range from as low as ten or eleven to as high as seventeen or eighteen on a side. It occurred to him that an increase in the number of teeth might well be an adaptation on the part of the insect to the tough skins of the larger domestic animals which offer abundant nourishment for little effort. In regions with great anopheline density and much cattle, competition would favour the strong, and in the struggle for existence multidentate insects would survive in greater numbers and propagate their kind. Those with a weak dental armature would be forced to live at the expense of man or other thin-skinned creatures, and would eventually become reduced in numbers and completely disappear. Roubaud[1] calculated that if the average number of teeth were between fourteen and fifteen it might be taken for granted that all the anophelines in the zone were feeding constantly on domestic animals and leaving man alone. If, however, the number of teeth should fall below fourteen, then man would be persistently attacked and malaria would spread in the community. If the average number of teeth should be found to be above fifteen, this would indicate intense competition on the part of the anopheles for food due to a disproportion between insects and cattle, and many mosquitoes would then be forced back upon man and thus become malaria carriers once more. Roubaud believed that groups with high dental indices tend to reproduce themselves if breeding and feeding conditions remain fairly constant, and have become in modern times fixed in their predilections to the extent of renouncing all contact with man. In 1920 Roubaud wrote, 'It may be said, therefore, that there are two physiological races of

[1] *Ann. Inst. Pasteur*, **42** (5): 553, May 1928.

A. maculipennis, one of malarious regions which has retained its primitive habits and continues to seek man, the other of non-malarious areas which has secondarily and more or less definitely directed its blood-seeking instincts towards animals.'

This theory has aroused considerable discussion and it cannot lightly be waved aside. Nevertheless, there are many weak points in it and in recent years some damaging evidence has been brought against it. Biologists have pointed out that half a century is a short period for the evolution of a new race which will continue to breed true in the presence of the original stock. Variation in the number of teeth occurs in all species of anophelines, and the same process of differentiation should be taking place in every region, and yet the phenomenon of anophelism without malaria is not linked elsewhere, as Van Thiel has observed, with a particular dental equipment. Furthermore, the counting of many teeth has brought only confusing results in the hands of most observers. For example, Sergent[1] has found a maxillary index of 14·4 for the *maculipennis* of the highly malarious Algerian plain—a value lying in the very centre of the supposed zoophilic range. Missiroli, Hackett, and Martini[2] in villages of hyperendemic malaria of southern Italy observed that the average number of teeth was exactly the same (14·2) for the anopheles captured in houses and those taken in stables. Van Thiel[3] caught a *maculipennis* mosquito with only fourteen teeth, avidly and without difficulty sucking the blood of a cow.

In a recent interesting research, Barber and Rice[4] have succeeded by means of the precipitin test in determining the source of the last blood meal of sixty-one anophelines, all infected with malaria. Of these only twenty-one (about one-third) had taken their last meal on man, the rest having

[1] *Bull. Soc. Path. Exot.* **15** (1): 29, Jan. 1922.
[2] *Riv. Malariol.* **12** (1): 1, Jan.–Feb. 1933.
[3] *Beih. Arch. f. Schiffs- u. Trop.-Hyg.* **30** (1): 67, 1926.
[4] *Ann. Trop. Med. & Paras.* **29** (3): 329, 5 Oct. 1935.

bitten horses or cows. This shows that the malaria vector had no difficulty in passing from one kind of host to another. As the matter stands at present, it is difficult to believe that the number of teeth has much direct influence on the amount of malaria. Roubaud, however, was the first to suggest the idea of a biological differentiation between different groups of insects in the same species leading to different host preferences, and this immediately began to prevail over the old idea that the anophelines were all alike and that their distribution between houses and stables depends upon the relative attractiveness of the two shelters.

The Dutch malariologists now reported that they had solved the mystery of malaria in Holland. Their explanation had nothing to do directly with zoophilism, since it was well known that all the Dutch anopheles greatly prefer domestic animals to man. Their studies had been oriented by the curious lack of correlation which we have already mentioned between the season of malaria infection in man and that of infection in the mosquito. Malaria has a very restricted distribution in Holland, and it is so mild as to be more of a curiosity than a problem, but, as Korteweg[1] has insisted for many years past, it is remarkable in that it occurs annually in advance of the mosquito season. First the annual malaria epidemic appears in man in the spring of the year, and then it attacks the mosquitoes which feed on man in summer and autumn, thus reversing the usual relation in malarious countries (Fig. 27, p. 215). There is in Holland no autumnal epidemic following the great anopheline activity of summer, as in southern Europe. Korteweg explained this by asserting that malaria in Holland is characterized by a long latency, and that the spring outbreak in man is evidently due to infections received during the previous autumn. This was, as a matter of fact, put to a crucial test by Schüffner, Swellengrebel,[2] and their

[1] *Nederl. Tijdschr. v. Geneesk.* **65**, 2nd half (12): 1485, 1921.
[2] *Kon. Akad. v. Wetensch. te Amsterdam*, **32** (7): 903, 1929.

friends, who allowed themselves to be bitten by infected mosquitoes between the 30th of October and 7th of November and had their primary attack without previous symptoms not less than eight or nine months later. All six came down with malaria between the 26th of June and 2nd of September of the following year. Hence it was evident that most of the malaria in Holland is contracted in one year and appears in the next. But how is it contracted? It is true that *maculipennis* breeds in profusion everywhere in Holland, but malaria transmission takes place, it appears, only occasionally and in one limited area.

Swellengrebel[1] now made an important observation. Not all anophelines go into hibernation on the approach of winter by migrating into unoccupied shelters and resting immobilized by cold until the spring. Many remain in warm stables and a few find their way into warm houses and stay there all winter, biting the inhabitants from time to time. At first it was considered that these were exceptions to the natural order and were merely comfort-loving individuals willing to sacrifice race-perpetuation to greed, for it was thought they could not survive until the spring. This was rather a blow to biologists, since it had been thought that only man was base enough to be anti-social to this extent. But it soon appeared that blood meals taken in winter by these mosquitoes do not stimulate their ovaries to activity, as is invariably the case in summer. Nature has relieved these insects temporarily of the obligation of reproduction. It was evident then that the semi-hibernators are not renegade members of the species, loath to abandon the flesh-pots and the warm shelters at the approach of cold weather, but rather a seceding race which has evolved an alternative method of passing the winter.

Here was Roubaud's idea of a biological difference between two groups of the same species in a different form, and thus was a mechanism for the transmission of malaria

[1] *Nederl. Tijdschr. v. Geneesk.* **68**, 2nd half (6): 750, 9 Aug. 1924.

created in an anopheline group which ordinarily was effectively 'deviated' by domestic animals from man. This separation of the reproductive from the nutritional responsibility of the mosquito was called by Swellengrebel 'gonotrophic dissociation', and to the appearance of this character in a certain biological strain of *A. maculipennis* was attributed the rather anomalous existence of endemic malaria in Holland. On measuring a great number of specimens of the insects found over-wintering in stables and warm houses, Van Thiel[1] found that their wings were on the average shorter than those of the hibernating group. It was announced, therefore, that *A. maculipennis* in Holland was divided into two races, the 'long-wings' and 'short-wings'. Zoophilism explained the general low level of malaria in Holland, semi-hibernation explained its persistence in certain localities where the 'short-wings' predominated.

It appeared, however, that if true this must be a rather localized phenomenon, for there was no doubt that the intense malaria of southern Europe, in large part of the severe *falciparum* type, rose to its peak in the late summer and was conveyed by the bites of mosquitoes which had been produced during the preceding months, and hence had nothing whatever to do with the hibernating habits of the anopheline vector. With respect to Roubaud's dental index it turned out that the smaller and more dangerous strain of *maculipennis* in Holland actually had more teeth than the harmless one, which was not according to theory. It confirmed, however, the genetic quality of the distinction between the two varieties, since had the difference in size been a mere modification due to environmental influences, the smaller mosquito would have had fewer and not more teeth than the other.

Acquainted with the work of Roubaud and of the Dutch group, Missiroli and Hackett[2] adopted a somewhat different

[1] *Beih. Arch. f. Schiffs- u. Trop.-Hyg.* **30** (1): 67, 1926.
[2] *Riv. Malariol.* **6** (2): 193, Mar.–Apr. 1927.

avenue of approach to the problem. If, in fact, there was a certain dissociation between anophelines and man, and if the amount of malaria was dependent on the degree of this dissociation, it was clear that the phenomenon was measurable, and the first step should be a quantitative determination of the contact between anopheles and man in hyperendemic, epidemic, and non-malarious areas. We were fortunate enough to have an excellent tool at hand for prosecuting this inquiry. This was the precipitation test devised by Uhlenhuth[1] for determining the source of the blood meal of blood-seeking parasites. His technique was modified to enable it to be used on a large scale, and thousands of anophelines were captured and tested in all parts of Italy.

The first discovery of importance was that the anophelines found in houses quite often contain animal blood. It was clear that after biting, *maculipennis* frequently takes cover in a different place to digest its meal and mature its eggs. Therefore the place of capture of an anopheline mosquito is not sufficient evidence of the source of its last meal. Secondly, upon analysing results the amount of malaria was found to be proportionate to the degree of contact between the anopheles of a given region and man. It was not in relation to the total production of *A. maculipennis* in the locality, since it was found that the proportion of anophelines which enter houses for the purpose of biting differs widely from region to region. Finally, it could not be shown that either semi-hibernation or number of teeth had much to do with malaria in Italy, which seemed rather to depend on the instinctive host-preferences of the local anophelines. All were able and willing to bite domestic animals, but where the insects were rather indiscriminate in their choice of hosts there was malaria, and where they seemed greatly to prefer animals there was not.

[1] *Arb. a. d. kaiserl. Gsndhtsamt*, **28** (3): 595, 1908.

We[1] pointed out the contrast, for example, between the little Tuscan valley, Valdichiana, in which malaria is absolutely unknown at the present time, and the delta of the Tiber not far from Rome, where Grassi had selected the village of Fiumicino for his early experiments because 100 per cent. of the inhabitants were infected. The following table gives the situation in a nutshell.

Relative number of A. maculipennis *with human blood found in bedrooms at Fiumicino and Valdichiana*

	Maculipennis *found in*		*Per cent. in bedrooms*	*Females caught in bedrooms*			
	bedrooms	*stables*		*total*	*with blood*	*with human blood*	
						no.	%
Fiumicino (14 farms)	113	321	26·0	90	57	48	84
Valdichiana (9 farms)	14	5,000+	0·3	4	4	0	0

From this it will be seen that there were a great many more anophelines in Valdichiana than in Fiumicino but that only one in three hundred entered houses in the former place, while one in four were taken from bedrooms in the latter. Since the mere presence in a bedroom is not a valid indication of the source of the blood meal, the precipitation test was applied and revealed the fact that in the malarious town almost 85 per cent. of the house anophelines and one in five of all the anophelines that could be found in any shelter contained human blood. In Valdichiana, however, not a single mosquito was found at that time, or on several subsequent visits, to have bitten man. This was all the more remarkable because the section of Fiumicino under observation consisted of completely new houses built within two years, according to modern hygienic standards, whereas the farm-houses of Valdichiana were medieval structures and

[1] Hackett, L. W., and Missiroli, A., *C.R. 2me Congrès Internat. du Paludisme*, **1**: 322, Algiers, 1930.

seemed to combine all the characteristics supposed to be attractive to European anophelines.

After many such studies carried on over a number of years, we were driven to postulate the existence of two biological races with different food habits within the species *A. maculipennis*, and it appeared to us that this might serve to explain most of the mysteries of malaria distribution in Europe. Such biological races, differing in physiology but not in structure, are well known among insects. Like the Dutch observers, we had no way of telling one race from another by microscopic examination, but we came to the conclusion that whatever the factor, environmental or instinctive, which determined the irregular and apparently haphazard distribution of these two kinds of *maculipennis*, it was this factor which also determined the presence or absence of malaria. We thought (though we were mistaken) that the presence or absence of a given race might have to do with the number of stables and domestic animals. The attractiveness of domestic animals for *maculipennis* in non-malarious regions was at least fifty times that of the malarious regions. But we were, and are, convinced that in southern Europe, at least, it is not any combination of attractive physical conditions such as darkness, warmth, dampness, and freedom from draughts, which impels a hungry *maculipennis* to enter a house, but instead the presence of a certain kind of food-supply to which by instinct it is drawn. This theory was announced at the Second International Malaria Congress at Algiers in 1930, and it aroused considerable discussion, criticism, and opposition.

It was a weakness of our contention that by no physical sign could one of these races be told from the other. It left the whole complicated situation in the air, at least in the opinion of systematic entomologists, who perforce ignore anything which they cannot label and put in a museum. We, therefore, persuaded one of our most able and searching critics, Professor Martini of Hamburg, to become a collaborator

and set out to discover some mark of identification with which to distinguish friend from enemy among the anophelines of Europe. The structures which have served entomologists best have been the larval hairs and the male terminalia. These were found to present a considerable range of variation, but no clear line of physical cleavage appeared between the *maculipennis* of highly malarious zones, and those of 'anophelism without malaria'.

In 1924, while Van Thiel was measuring mosquito wings in Leiden, a retired inspector of public health in Italy, Falleroni,[1] began to breed anopheles as a hobby. He was struck by the beauty and diversity of the various patterns on the upper surface of the eggs, and he noted that the same female always laid the same kind of egg. He collected females from various parts of Italy and was able to assemble five general types into which all the eggs he had seen could be made to fall.[2] He classified them all, however, as either dark eggs or grey eggs, and named them *messeae* and *labranchiae* after two of his friends in the Health Department, Dr. Messea and Dr. Labranca. He drew some excellent figures of the egg-types and had them published, but they did not attract the attention of anybody. The different patterns of anopheline larvae had long been noted and discussed by entomologists. They had always proved to be completely without significance, like the spots on mongrel puppies. This indifference to the egg-types on the part of entomologists now appears almost incredible. Only about four years before, *elutus* had been separated from *maculipennis* as a new species, on the basis of one or two minor differences in the adult, which were often hard to make out in wild-caught females of uncertain age. The egg of *elutus*, however, was found to be quite different from that of *maculipennis*, and in practice entomologists used this character for differentiating one group from the other. It is curious

[1] 'Studio sugli *A. maculipennis* delle Paludi Pontine' (Recanati, 1924).
[2] *Riv. Malariol.* **5** (5–6): 553, Sept.–Dec. 1926.

that in all of these observations no one but Falleroni had paid any attention to the fact that there are several different types of eggs in the *elutus-maculipennis* group, and not merely two.

Seven years after Falleroni's discovery, which he and the rest of the world took to be a mere eccentricity of nature, the egg-types came to the attention of Martini, Missiroli, and Hackett,[1] who took them under consideration in their search for a structural difference between the two hypothetical races. Among the other exhibits from malarious and non-malarious localities, eggs were collected from female mosquitoes caught in stables and in houses. All of Falleroni's patterns, and only those patterns, appeared in various mixtures. But Missiroli called our attention to the fact that, while all were reported at one time or another from malarious regions, two were always missing from those in which malaria had disappeared: the grey egg of *elutus* and the light dappled egg which Falleroni had called *labranchiae*. This seemed worth looking into, and hypopygial spines and palmate hairs were set aside for a time while careful egg surveys were made in Italy and Germany. It was very encouraging to find that Falleroni's forms were also sufficient for northern Europe. They were not all represented there, for only three different kinds of egg were found north of the Alps.

The egg of a mosquito is a beautiful and delicately ornamented object, with two fan-shaped structures full of air on either side, called floats, to balance them in water. The outer coat is set with a coarse, thick pile, like velvet, which under the microscope resembles little columns, some short, some tall, some flat, some rounded on the top. The design on the egg is produced by the type and arrangement of these *columellae*. Where they are high, with rough and exuberant tops, the light is refracted, giving them a grey and sometimes frosty white appearance. But in certain spots the

[1] *Arch. f. Schiffs- u. Trop.-Hyg.* **35** (11): 622, Nov. 1931.

papillae are smooth on top, reduced in size, and, at times, almost suppressed, lending a transparency to the outer coat and allowing the dark undersheath to show through and produce the characteristic surface markings of the egg. The *elutus* egg is a uniform bright grey without any floats at all; the *messeae* is covered with angular dark blocks and two characteristic black bars, which cross it symmetrically and divide it into thirds; *labranchiae* is a fattish egg with fine cuneiform markings along the edges and with minute floats. The three other forms, which now seemed to us to be quite as distinct types as those named by Falleroni, are no less easy to distinguish, as can be seen from the photographs, one being mainly black, irregularly flecked with white, another dappled with dark spots, and the third marked with two simple bars against a field of frosty white. These were subsequently called *melanoon*, *atroparvus*, and *typicus* (the last a nickname for *A. maculipennis* type).

If the egg-types were not infinitely diversified, neither were they distributed at haphazard. A batch of mosquitoes caught in a given shelter did not present a heterogeneous mixture of all the known types, like chickens in a peasant's yard, but certain types were characteristically found in certain localities. It occurred to us almost at once that they must be tied up with the physical geography of the region. Of the three types of northern Europe, one was found mainly in the hills, one in the bottom lands of the great river valleys, and the third principally along the coast. But the most important finding was that there are zones in which each of the six types[1] occur virtually alone. This was essential to the study of the instincts and behaviour of the presumed races because there was still no way of telling the adults apart. If the *A. maculipennis* in Europe were really six different mosquitoes instead of one, occurring in unknown mixtures, their bionomic characters could not be

[1] In this discussion *elutus*, though recently given the standing of a species, will be treated as a variety of *A. maculipennis*.

FIG. 4. SOME EGG-TYPES OF *ANOPHELES MACULIPENNIS*
In the upper row are the so-called barred eggs of the cattle feeders: *melanoon* (black), *messeae* (richly patterned), *typicus* (two bars on a white field). In the lower row are the malaria vectors and brackish-water breeders, with a more uniform pattern: *atroparvus* (Atlantic coast and western Spain), *labranchiae* (western Mediterranean spreading from Sicily), *elutus* (dangerous anopheline of the Balkans and the Near East)

studied in nature unless we could find them somewhere in pure culture. This it was now possible to do, and the fact that each of the forms in these segregated natural colonies had bred true for generation after generation was a strong confirmation of our hypothesis that each egg-type stands for a pure genetic line within the species *A. maculipennis*. We pressed forward to discover whether the egg findings might not substantiate those more important biological differences which seemed to govern the distribution of malaria. All these discoveries, which appeared to us enormously suggestive and important, wakened outside interest only in Holland, where the Dutch observers had come to similar conclusions by quite a different route.

The Dutch knew that the *maculipennis* of Holland would breed not only in fresh, but also in moderately salt water, and Van Thiel thought that it might be the different breeding conditions which produced mosquitoes differing in size, those from the brackish waters being smaller than the others. He had proved that there was a difference in size by measuring a great many wings, both in nature and in bred-out specimens, but he could not be sure whether it was a modification produced by the salinity or a true genetic character transmitted by heredity. It was a question not easy to decide, since there is an extraordinary variation in the size of mosquitoes of the same species, dependent in part on the nourishment of the larvae and in part, as Martini pointed out, on the temperature of the water in which the aquatic stage of the insect has been passed. Thus Shannon found in Macedonia that the *elutus* of early spring might be three times the size of the summer insect.

Van Thiel also reported that the 'short-wings' were darker in colour than the others, but Achundow[1] showed that colour is not a dependable hereditary character. By bringing up the larvae from the same batch of eggs in different coloured bowls he produced insects of varied shades and

[1] *Arch. f. Schiffs- u. Trop.-Hyg.* **32** (11): 547, Nov. 1928.

tones; he even thought that the colour of the breeding-place had some effect upon the size of the insect. The thing, however, which made Van Thiel suspect that he was dealing with a natural variety rather than a modification, was the fact that the smaller mosquito had more teeth than the larger, which was contrary to Martini's rule that, like wing-length, number of teeth is correlated with size. But this was a biometric character which could only be determined by counting and averaging a large number of specimens. Neither by size, colour, nor number of teeth, therefore, was Van Thiel able to identify any individual specimen.

Swellengrebel[1] and his colleagues in Amsterdam began to study the biology of the brackish-water anopheles, and came to Van Thiel's assistance by showing that the 'short-wings' do not hibernate like the majority of *maculipennis*, but spend the winter in shelters warmed by the presence of man or domestic animals, and furthermore, that it is their habit to mate indoors without the usual dance of the males. They could thus without difficulty be established as a captive colony in the laboratory which would reproduce itself indefinitely. Their behaviour, more than any physical differences, seemed to distinguish them from the rest of their kind, and though Van Thiel gave the 'short-wings' the name *atroparvus* ('the small black'), they seemed more of a biological race than a variety, since the physical characters were insufficient for purposes of identification.

The Dutch had been labouring under the handicap of not being able to separate their races except by their behaviour in winter. Identification by egg-type was at once tested in Holland. The results were eminently satisfying to us and to the Dutch. The short-wings (*atroparvus*) laid only one kind of egg, which was precisely like that found by Martini on the north German coast. This was perhaps to be expected, but it came as a distinct surprise to us to find that it was also exactly like an egg which we had found in north

[1] *Kon. Akad. v. Wetensch. te Amsterdam*, **30** (1): 61, 18 Dec. 1926.

Italy, in a part of the delta of the Po lying below sea-level but reclaimed years ago by diking and pumping. No southern area could possibly have been found which more resembled a Dutch 'polder'. This small population of Italian *atroparvus* would also mate in captivity, a result never obtained with any south Italian form. At the coming of autumn, to our complete satisfaction, these lowland breeders refused to follow their companions into hibernation but remained semi-active in the stables throughout the winter, occasionally biting animals but ripening no eggs until the spring.

We now felt sure that *maculipennis* was not a homogeneous species, but a group of at least six widespread varieties,[1] differing more in biological than in physical traits. As a matter of fact, setting aside the biometric differences to which a value can be given only after measuring a considerable number of cases and averaging the results, only three strictly morphological characters have ever been found to aid in classification of individual specimens: the egg type, a larval hair discovered by La Face[2] in 1931, and the shape of a spine on the male terminalia, described by De Buck, Schoute, and Swellengrebel[3] in 1930. Unfortunately the last two showed such a paucity of forms with so much overlapping that they were not sufficient in themselves for the classification of any given specimen. Females could, however, be identified by their eggs, and their distribution seemed to be determined broadly by climate (only three were found north of the Alps) and locally by certain physical features of land and water. Thus, of the three northern races, one was a coastal brackish-water breeder, and of the two fresh-water races one seemed to like marshy river valleys and the other hill streams. Each race appeared to be represented in many different and widely separated sections

[1] Hackett, L. W., *Trans. Roy. Soc. Trop. Med. & Hyg.* **28** (2): 109, Aug. 1934, and *Quart. Bull. Hlth. Org. L.o.N.* **3** (4): 654, Dec. 1934.
[2] *Riv. Malariol.* **10** (6): 673, Nov.–Dec. 1931.
[3] *Riv. Malariol.* **9** (2): 97, Mar.–Apr. 1930.

of the vast range of *A. maculipennis*, and two or more races often occurred mingled together in the same area, so that they did not resemble at first sight what we are accustomed to call geographic sub-species, which are normally isolated from their parent stock by some physical or other environmental barrier that protects their distinctive character by preventing any interbreeding with the species from which they have become separated.

The beginnings of an investigation into the bionomic traits of the races revealed at once profound differences in mode of hibernation, sexual behaviour, and even host preferences.[1] We began to suspect that we were on the track of that elusive 'factor *x*' which enabled malaria to spread in one area, and reduced it to impotence in another.

[1] Hackett, L. W., and Missiroli, A., *Riv. Malariol.* **14**, sec. 1 (1): 45, Jan.–Feb. 1935.

III

ANOPHELISM WITHOUT MALARIA

Trattasi ormai di problemi che sono al confine della più alta biologia e quindi nessuna meraviglia se gli studi non portarono ancora completa luce. . . .
A. CELLI, *La Malaria* (1910)

SYSTEMATIC entomologists seemed rather averse to setting up at once a number of new subspecies on the sole basis of egg or behaviour patterns in a group of mosquitoes otherwise indistinguishable. The geneticists, on the other hand, found the proposal neither novel nor objectionable. By definition a species must differ from every other species in certain structural peculiarities which its members possess in common. But the geneticists have their biological races which, according to Thorpe,[1] exist where 'the individuals of a species can be divided into groups occurring in the same locality and showing definite differences in biology but with structural differences either very slight and inconstant, or completely absent'. Naturally such groups do not interbreed, for otherwise the differences could hardly be maintained. How is it then with the *maculipennis* groups, two or three of which are usually found mingling in the same locality? Do the males distinguish between the females which look so much alike, and refuse to mate with those of an alien race?

This question is of the greatest importance, but it proved at first difficult to answer. *Anopheles maculipennis* when mating observes in general the ritual of the swarming of the males which occurs out of doors over some fixed object such as a haystack or gable, beginning, as Shannon happily records, just as Venus begins to shine in the west. At first

[1] *Proc. Assoc. Econ. Biologists I. Ann. Appl. Biol.* **18** (3): 406, Aug. 1931.

the males are seen in circling groups of three or four, attracted by each other's humming, and these, falling under the ascendancy of larger assemblages, coalesce to form vibrant, ballooning swarms exquisitely sensitive to sound, so that if you stand under them and hum loudly the *maculipennis* males become completely disoriented. The swarm bursts like a bomb and disappears, only to reform again in the same place as the noise ceases. To these swarms the females are now irresistibly drawn; they dash in, each seizing a dancing male, and fly off with him in the act of copulation. Males do not swarm in cages, and yet, in order to find out whether the different races breed true, and what if any are the results of intercrossing, selected males and females must be induced to mate in captivity. None of our attempts were successful either in Rome or in the Balkans. Cages were made larger and larger in the hope of inciting the males to swarm, until finally in Albania we constructed a huge screened space, thirty feet long and twenty feet high, containing a small house and calf stable, a tree, a garden, and an attractive natural pool; but although we liberated in it many thousands of *maculipennis* of both sexes bred out in the laboratory, we were not able to establish a self-perpetuating colony.

We were somewhat annoyed to learn of occasional successes in other countries. In England Harold,[1] in 1923, had obtained three successive generations in cages about twenty inches on a side. We heard that at least three different insectaries (Hamburg, London, and Navalmoral in Spain) had had stock broods of *maculipennis* which maintained themselves for a time without any special difficulty. It was the Dutch observers[2] who first discovered, about 1930, that only their 'short-wings' would mate in captivity, and the others would not. When this race was afterwards identified

[1] *Jl. Roy. Army Med. Corps*, **41** (4): 282, Oct. 1923.

[2] de Buck, A., Schoute, E., and Swellengrebel, N. H., *Riv. Malariol.* **9** (2): 97, Mar.–Apr. 1930.

through its egg type with *atroparvus*, it was clear that all the successful breeding experiments had been carried out with *atroparvus* and the other five races were refractory. It was our ill fortune that *atroparvus* does not occur in southern Italy, nor in any of the Balkan countries where we had our field stations. *Atroparvus* males do not swarm, but couple with the females indoors on the walls of stables and other shelters, and this has now been seen to occur in nature by a number of observers. This would be an advantage to a seacoast race where strong winds might often prevent the dance of the males. Roubaud has proposed the term *stenogamous* to describe those forms which will mate in confinement, and *eurygamous* for those requiring the wide open spaces. The true distinction to be drawn, however, is whether the males must swarm before mating, and whatever the impediment may be in certain cases, it is not exactly lack of space. *Elutus* dances and mates in a very small room, and I have seen *A. superpictus* males swarming in a box 20 centimetres cube. It might be as well to forget the terms 'eurygamous' and 'stenogamous', for they only serve to confuse the issue.

De Buck, Schoute, and Swellengrebel,[1] however, immediately discovered something of even greater importance to the solution of our problem: *atroparvus* males could frequently be induced to mate in captivity with females of *messeae* and with those of the other races. The reciprocal mating would also occasionally take place; that is between *messeae* males and *atroparvus* females, and it is a very singular thing that the two sexes of *messeae*, which will not copulate with each other in a confined space, will do so with individuals of another race.

The results of such intercrossing were awaited with the greatest interest, but in no case, as it turned out, was a fertile F_1 (first filial) generation produced. However, even

[1] *Riv. Malariol.* **13**, sec. 1 (3): 237, May–June 1934.

so the experimental matings had different degrees of success, as shown below:

Crossing	*Result*
atroparvus × *messeae:*	eggs sterile, or larvae die without hatching, or if they hatch, all die at an early stage.
,, × *elutus:*	larvae not viable, but succumb at an advanced stage.
,, × *typicus:*	eggs produce healthy but sterile insects of F_1 generation (male and female reproductive organs undeveloped). See Fig. 5.
,, × *melanoon:*	F_1 generation healthy: half the females have normal ovaries, but males are all sterile.
,, × *labranchiae:*	F_1 generation healthy: all females but only a part of the males with normal organs of reproduction.

The results were thus of two different sorts: either no viable F_1 generation could be obtained, as is the case, for instance, in attempted crosses between the water buffalo and the cow; or healthy hybrid offspring could be bred from the eggs, but they were sexually defective and hence unable to continue the race, as in the case of mules which are usually, but not in every instance, sterile. The conclusion is that in Holland, where three races intermingle, the crossing of the 'short-wings' (*atroparvus*) with the 'long-wings' (*messeae* and *typicus*) is definitely prevented in nature by a barrier of mutual sterility.

This at once furnished a way of comparing the *atroparvus* of Holland with the race laying the same kind of egg in Italy, which as we have seen is found occupying the lowlands reclaimed from the sea in the delta of the Po. Corradetti,[1] in our laboratory, crossed Italian *atroparvus* with the other *maculipennis* races of Italy and obtained exactly the same results as those of the Dutch entomologists, which confirmed not only the identity of the *atroparvus* races, but indirectly that of all the others. The males of other races

[1] *Riv. Malariol.* **13**, sec. 1 (6): 707, Nov.–Dec. 1934.

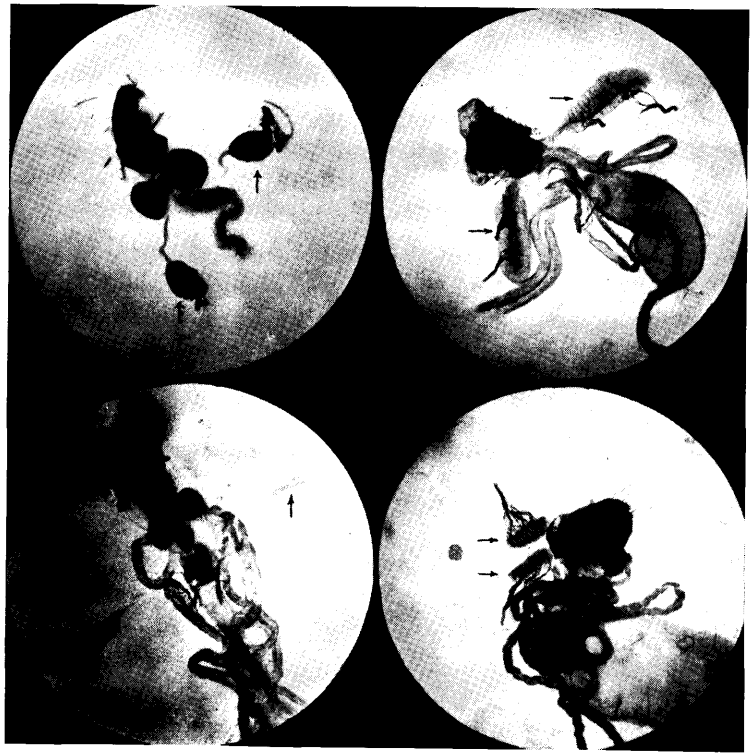


FIG. 5. DISSECTIONS OF NORMAL AND HYBRID MALE AND FEMALE *MACULIPENNIS* MOSQUITOES

Above, the arrows point to the normal testes (left) of a male *atroparvus* and the normal ovaries (right) of a female *typicus*. Below are shown the sterile hybrid products of a cross between the two races, with undeveloped testes and ovaries

(*After* Corradetti)

refuse to co-operate in cross-breeding experiments, but since they will not even fecundate females of their own kind in captivity, we cannot tell whether this is due to a natural barrier between races or to a state of confinement incapacitating to a 'eurygamous' insect. Nevertheless their diverse responses to insemination by *atroparvus* reveal profound differences among them. Thus *atroparvus* appears to be especially remote genetically from *messeae* and *elutus*, less so from *typicus* and *melanoon*, and least of all from *labranchiae*, with whose range, however, its own does not coincide to any extent.

These experiments had the unexpected consequence of lifting *atroparvus* (and with it the other forms) at one bound to the logical status of true species. The question of mutual sterility is in fact the severest test of the specific nature of differences between varieties. Lack of intercrossing makes a group (according to Walsh) equal in value to a species which is distinguishable on structural grounds, yet it is not easy to assign to it a definite place in systematic entomology. Thorpe believes that we cannot without endless confusion include biological races and morphological species in one systematic category. The *maculipennis* groups are, it is true, something more than biological races, since we have at least the characteristic egg patterns to distinguish the fertilized females, but systematic entomologists accept such a character with the greatest reluctance as long as the adult lacks any identification mark which would entitle it to a reserved place in their orderly collections.

At this point the geneticists again come to our aid, if only with an hypothesis. Shull,[1] in a recent discussion of modern evolutionary theory, points out that while variations arise through mutation, or changes in the nature or arrangement of genetic units, Bateson rejected mutations as evolutionary because of their nearly universal fertility with the parent types. How could species which are usually intersterile

[1] *Science*, **81** (2106): 443, 10 May 1935.

arise from a common stock through changed individuals which were at every step fertile with one another and with their parent types? Geographic isolation does not suffice to explain the mutual sterility, partial or complete, which arises between groups along with their visible differences, though some biologists have taken refuge in the belief that geographic isolation once existed where none can now be seen. The causes cannot be found in the environment; the search is now being made among genetic phenomena. Are there sterility genes? Sterility must originate early in the process of separation, or even before any other modification commences. It is probably one of the primary reasons for the splitting of species, removing them from the levelling influences of hybridization. In other words, we are now invited to look upon sterility not as the final result or accompaniment of accumulated mutations, but as the first mutation of them all and the beginning of speciation.

It will hardly be useful here to pursue our problem any farther into the debatable land of the origin of species. We are faced with the *fait accompli* of a series of mutually sterile groups in what may once have been a homogeneous species. Whether we call them varieties or races, we have the right to think of them as distinct species. In this respect as in others our concept has changed since Darwin's time, when the Linnaean species was a clear-cut unit set unmistakably apart from all other units. This was an oversimplification of the natural affinities, which are of every degree. Goldschmidt[1] remarks that, while one nematode species may differ from another in every cell, it is almost impossible to tell the skeleton of a lion from that of a tiger. In a widespread '*Formenkreis*' some varieties will have acquired structural differences by which they can be labelled and placed in museums, but these will form an exceedingly incomplete family group. Some strains will differ from the stock in purely biological traits which leave them indistinguishable except for their

[1] *Science*, **78** (2033): 539, 15 Dec. 1933.

behaviour. Some, like the *maculipennis* races, will show the beginnings of a structural differentiation. The systematists who classify our species have not kept pace with biological progress. Their picture of an anopheline species is an inadequate representation of the reality in nature. The epidemiologist therefore is inclined to follow the geneticist, for to him behaviour is everything and morphology is only a tool.

It will help us to understand the diversified behaviour of the varieties of *maculipennis* if we can forget their extraordinary physical similarity and treat them as different species. We see at once how they can be so unlike in instinct and habits—some hibernating, others not; some mating indoors like stegomyia, others swarming like tipulids; some breeding in saline waters, some in fresh-water marshes, and others preferring spring-fed streams or pools. We would expect to find species differing from one another in these ways.

It would naturally be of the utmost importance to malariologists to be able to show that the races differ also in their feeding habits. Years ago Roubaud suggested that under the pressure of competition for food a group of *maculipennis* might in certain situations develop stronger piercing organs to enable them to attack thicker-skinned animals and that such a 'zoophilic' group, passing on its special adaptations to its descendants, would thereafter leave man alone and thus diminish the amount of malaria transmission. The discovery of the races of course indicated a new line of approach to the study of host preferences.

At first sight it would not seem a difficult thing to determine what animal or animals any given insect like an anopheline would prefer to feed on. Mosquitoes of a given species or race could be loosed in a big room in which specimens of the likely hosts, such as man, horse, cow, dog, &c., had been assembled and careful note could be taken of the distribution of the bites. It is the sort of thing Noah could

have settled once for all had he been conscious of his exceptional opportunities. In fact, Bull and Root[1] once did this very thing to discover the biting propensities of *A. quadrimaculatus*, recapturing the mosquitoes next morning and determining the source of the blood meal for each individual insect by subjecting its stomach contents to the well-known medico-legal test used to find out the origin of suspicious blood-stains on clothing. The experiment did not give any clear results, since the mosquitoes, faced with an unusual variety of unprotected victims, went at them without discrimination of species, although certain individuals were preferred over others.

The physiological entomologist now tells us that there are a number of pitfalls for the unwary in such a test. In the first place captive insects are not normal insects. Some are likely to be famished if they have been kept for any length of time, and hence ready to overcome almost any difficulty or repugnance to obtain blood; others, in an unnatural situation or physiological condition, may refuse to bite at all, or at least to reveal any characteristic inclinations. But there is a subtler reason for rejecting evidence gathered in this way as proof of an instinctive preference for a particular host. Insects are largely governed in their various activities by external stimuli. Conditions of light, temperature, humidity, and other physical factors undoubtedly play a great role in what seem to be the purposive movements of mosquitoes, and these may well influence their biting activities. Any one who has worked with anophelines knows how capricious they are about feeding. Ross mentions this as one of his early difficulties in trying to infect mosquitoes from patients in India. He found that they would often consent to bite only if the air were saturated with moisture by placing a wet sheet over the cage while it was in contact with the patient. Boyd keeps his mosquitoes on ice until

[1] *Am. Jl. Hyg.* **3** (5): 514, Sept. 1923; also *Am. Jl. Hyg.* **4** (2): 109, Mar. 1924.

the last moment and applies them suddenly to a pink, moist, and warm spot produced on the patient by a hot-water bottle. Biting in such cases seems like an automatic reflex, hardly under the instinctive or intelligent control of the insect. James has observed anophelines in cool stables in England dropping down from the rafters upon steaming horses coming home in the evening from their work. Many of these contained blood still undigested from the night before, but they appeared unable to resist the powerful stimulus to feed again.

Now the physical conditions immediately surrounding the insect and influencing its elective movements—such as the illumination, the humidity, the temperature, and the air movements of a day-time resting-place, or of a shelter chosen for hibernation, or of a stable or bedroom during the feeding-hours—would not be the same as those reported for the district by the local meteorological station. They are referred to therefore as 'microclimates', and more often than not they escape our attention, for it is clear that we shall learn very little about the moisture conditions affecting insects living under the leaves on the forest floor by whirling a hygrometer in the air over their heads.

A favourable atmosphere for biting may then at times envelop all kinds of animals. For instance, milkmen in Lombardy are frequently bitten by anophelines in the cow-barns as they begin their work at three or four o'clock of a summer morning, but scarcely ever in their unscreened bedrooms. Therefore, when we are tempted to proclaim 'instinctive choice' as the mainspring of action in a natural or a cleverly devised situation, entomologists have recently begun to counter with 'microclimate'. This is a question not easy to settle, for the influence which prevails in any given case—inward urge or outward stimulus—depends probably on the physiological state of the insect at the moment, and that we are sure is always in flux. Thus it is unexpectedly difficult to plan a crucial experiment which

by eliminating all microclimatic influences will disclose the food preferences of the different races.

Perhaps the most ingenious test was devised by Barber and Rice. A cage built like a flat drum was interposed between the uncovered abdomen of a man and the shaved flank of a calf. The mosquitoes used were a mixture of *elutus* and *maculipennis* (*messeae* and *typicus*) which had recently laid eggs and might be supposed to be in a normal mood for another meal, but not famished. The mosquitoes were liberated in the drum and had their choice of human blood on one side and animal blood on the other, only a few centimetres apart. The results of several tests were as follows:

	Bit man	*Bit calf*
elutus	45·2%	45·2%
messeae and *typicus* . .	15·7%	79·3%

Elutus was clearly indifferent as to the source of its blood-supply, but the other races seemed to have a bias for the calf. We can at least say that under the same experimental conditions the races behaved differently.

How is it in nature? Where two or three races occur together such differences would be apt to stand out, if any existed. It happens that at Diamantina on the river Po, *elutus* is found mingled with a population of more northern *maculipennis*, principally *messeae*, *typicus*, and a few *atroparvus*. In 1926 La Face[1] recorded the following catches:

	Bedrooms	*Stables*
A. maculipennis (3 varieties)	3	478
A. elutus	158	226

Here is a pronounced difference between one group and another, but at the same time here is another pitfall.

It used to be generally assumed (though without foundation) that anophelines caught full of blood in bedrooms had bitten man, and a great deal of epidemiological evidence was

[1] *Riv. Malariol.* **5** (1): 44, Jan.–Feb.; and (4): 381, July–Aug. 1926.

accumulated on this basis. We now know that the places which anophelines choose for day-time shelter often give no clue to where they go foraging for blood at the hour when, as Dante said, the 'fly gives way to the mosquito'. Such a clue was provided when Uhlenhuth discovered the precipitin test, which we have already mentioned, for determining the nature of blood-stains of unknown origin. Uhlenhuth himself employed the test to verify the hosts of blood-sucking insects. It was used by Missiroli and myself on a large scale to determine the amount of contact between anophelines and man in various regions. Now, with the discovery of the races, this blood test has become one of the most useful tools of epidemiological study in malaria. The procedure which used to be laborious and costly has been improved by Rice and Barber[1] so that large numbers of blood specimens from mosquito stomachs can be analysed rapidly at slight expense. At once the great mobility of the anophelines after feeding was brought to light. Even in malarious regions of southern Europe it is unusual for as many as half the anophelines caught in bedrooms to contain human blood, and in non-malarious regions most of the *maculipennis* which enter houses do so not for food, but to seek shelter during the digestion of blood-meals taken somewhere else. *Superpictus*, on the other hand, although it readily goes into houses to bite man, greatly prefers to roost in stables, so that without the precipitin test to aid us we might draw the most erroneous conclusions from our comparative catches in human dwellings and in animal quarters.

Every technical advance of this sort is a highway into new country, for our knowledge of the activities of anopheline mosquitoes in nature is nearly all surmise and deduction. We see them swarming on rare occasions just as the light fails, and we often surprise them at their food with our pocket flash-lamps, but what goes on in the open air during the night is in large part successfully concealed. The rising

[1] *Jl. Lab. Clin. Med.* **20** (8): 876, May 1935.

sun gives the signal for a vast scurrying for shelter, and a certain number then become the objects of our curious observation as they rest in blank immobility for twelve or fifteen hours until the darkness comes again to set them free. We have learnt how to stain mosquitoes different colours so that we can recognize them again if we should see them. But it is the precipitin test more than any other which has emancipated us from complete dependence on captive insects and the artificial conditions of the laboratory. We labour under one peculiar handicap with *maculipennis*: we cannot ever determine the race of the mosquito, and the source of its blood-meal, on the same specimen. When the eggs are ripe enough for classification there is no fresh blood left for testing. We must work then with *elutus*, which can be identified, or with a population known to be of pure race, or with mixed populations from which certain races are known to be absent.

This has not proved to be difficult or confusing in practice. We have already accumulated data on the last suppers of thousands of anophelines of different species and races. And just as the species differ from one another in the extent or order of preference in which they resort to various possible hosts, so do the races. In the well-watered valleys and uplands of Tuscany abounding in the varieties *messeae*, *melanoon*, and *typicus*, it is the rarest thing in the world to capture a specimen, even in bedrooms, which contains human blood. In that region and with few exceptions throughout Europe these races feed habitually on the larger domestic animals. Other forms are less specialized. In southern Italy and Sardinia, where *labranchiae* prevails, from 10 to 20 per cent. live on human blood, while in Greek Macedonia every third *elutus* captured will have been biting a man. Postponing for a moment any discussion as to the nature of the determining influences which bring about this dissimilar distribution of the various races among their accessible hosts—whether it is pure instinct or difference

in microclimatic sensibility, or more likely a mixture of both in varying proportion—the fact remains that for the most part the division is according to race and not according to individual, or to region.

This point is so fundamental to the association of certain races of *maculipennis* with the spread of malaria that it is worth while pausing a moment to look at the sort of data on which the assumption rests. The most exhaustive study of the kind has recently been published by Barber and Rice, from a very malarious region in Greek Macedonia where *elutus*, *typicus*, and *messeae* occur together. The authors obtained over 13,000 positive blood tests on these varieties, with the following results:

	Elutus	*Maculipennis* (2 varieties)
Caught in houses:		
Positive tests	3,890	1,798
With human blood	2,439 = 61·3%	381 = 21·2%
Caught in stables:		
Positive tests	2,855	4,607
With human blood	213 = 7·5%	22 = 0·5%

In the houses three times as many blooded *elutus* as *maculipennis* had bitten man, and in the stables the ratio was 15 to 1. Of all the *elutus* captured, 40 per cent. contained human blood, but of all the *typicus* and *messeae*, only 6 per cent. These are indices derived from unweighted samples of the anopheline population, but since it is not unreasonable to suppose that more mosquitoes were overlooked outside houses than inside them, they probably do not exaggerate the difference between the two groups. There are other data pointing the same way. For instance, of the total collections made by Barber and Rice in two or three years, 40 per cent. of the *elutus* but only 26 per cent. of the *maculipennis* were taken in houses, and if this be considered in connexion with the blood tests of the previous table, *elutus* would seem to be five times as keen on human blood as the other two races.

If this is true we ought to find many more *elutus* infected with the malaria parasite than *messeae* or *typicus*. Pains and dexterity are required to remove the salivary glands of a mosquito and to verify the presence or absence in them of the malaria parasite. Only a malariologist can appreciate the labour involved in dissecting and examining in this way 37,000 anophelines, yet Barber and Rice[1] have given us the following table, built up during three years of patient investigation. It is not often that the results of such an imposing body of research can be expressed in such small space:

Elutus:	dissected:	22,200;	infected:	1·29%
Maculipennis:	,,	14,713;	,,	0·07%

Nineteen infected *elutus* were found for each infected *maculipennis*. *Messeae* and *typicus* were evidently the victims rather than the agents of malaria infection. It naturally occurred to the authors that *maculipennis* might be less susceptible to malaria infection than *elutus*, for species tend to differ in this respect. *Superpictus*, for example, is almost three times as easy to infect with malaria as *maculipennis*. However, when they applied a large number of *elutus* and *maculipennis* to the same malaria carrier at the same time, almost exactly the same percentage (20 per cent.) became infected at one feeding.

Malaria does not necessarily occur, therefore, where susceptible mosquitoes exist in effective numbers, but only where the kind of anopheline is present that persistently enters houses to feed on human beings. This is hardly a new thought as regards the species of anopheles in general. It is almost an axiom (as I once wrote)[2] that 'the fundamental similarity between the diverse kinds of anophelines which transmit malaria in the world is that they all readily bite man and bite him repeatedly however widely they may differ in other bionomic characters'. We must now extend this rule (or rather its converse) to cover the different races

[1] *Ann. Trop. Med. & Paras.* **29** (3): 329, 5 Oct. 1935.
[2] *South. Med. Jl.* **22** (4): 367, Apr. 1929.

into which a species may be resolved. However alike these may be in almost every character, they may take their blood-meals in different places and from different hosts. In eastern Macedonia it is *elutus* which spreads malaria while *messeae* and *typicus* have virtually no hand in it, for, in a region where we may say malaria is universal among the inhabitants, not one in a thousand of these two races becomes infected. In the same way *labranchiae*, and not the concomitant *melanoon*, is the malaria agent in southern Italy and Spain, while in Holland it is *atroparvus* but not *typicus* or *messeae*.

Over most of Europe then (where there is no other carrier species) malaria follows the distribution of the races of *maculipennis* that live at the expense of human beings, and these are *elutus*, *labranchiae*, and *atroparvus*, all normally brackish-water breeders. Malaria tends therefore to hug the coastlines, and is not usually found in inland fresh-water areas inhabited by other races. This rule is supported by certain exceptions, for while there are coastal zones (such as that around Naples) quite free from malaria, it has been found that all the breeding-places are fresh and produce only harmless varieties; and where malaria exists in inland places, it is often associated with salt lakes or springs, as at Diamantina in the valley of the Po. Martini was surprised to find *atroparvus* sparsely represented in the *maculipennis* population about the Prestersee, an apparently fresh-water lake near Magdeburg, far from the ocean. However, he noticed here and there along the shore an occasional plant characteristic of brackish water—a survival, like the insect, of a salty epoch in the lake's history. It is striking how salt crops up in connexion with malaria. Pittaluga noted, long before the races were thought of, that 'in the province of Alicante is a territory where there used to be extensive salt marshes and where in recent years very severe epidemics of malaria have taken place'. I imagine, if we should go to Alicante, we would still find *labranchiae* there. Missiroli, called to investigate a queer isolated area of endemic malaria

in central Sicily, found it bordering on a brackish lake. Nevertheless, as we shall see, salt is not the perfect clue to malaria, as we once thought. It becomes less and less trustworthy as we go south, and in the next chapter we shall have to reconsider the whole question of saline-water breeders. But this will not affect our general conclusion, which is that the endemic centres of malaria to which it contracts in times of adversity are those places where the carrier races are most firmly entrenched, and that the strongholds of the non-vectors, in the north as in the south, are the much discussed areas of 'anophelism without malaria'.

I should like to be able to bring the story to a close at this point with the problem solved, the villains run to earth, and most of the malaria paradoxes cleared up. Certainly with the aid of the egg patterns, mosquito dissections, and the blood test we have got hold of the essential facts in the case. Nature was able to maintain the mystery as long as she did only by contriving to have all the principal characters look exactly alike, a device which no self-respecting writer of detective fiction would deign to use. But while the main structure of our present theory is just as we have stated it above, the sharp outlines are beginning to dissolve under closer examination. In other words, we are now well into the second stage of a biological investigation of a new field, when more intensive research begins to reveal difficulties and inconsistencies and not a few examples of flat disobedience of the rules.

Until Martini and Zotta[1] made their survey of Roumania in 1933 no region was known in any part of Europe in which *messeae*, *typicus*, or *melanoon* was associated with endemic malaria. Since then some malarious villages on the Danube just above its delta have been found to lie in a zone of unmixed *messeae*. There was also another small area in which *typicus* was incriminated. The malaria was mild and *vivax* in type, but it was endemic—in other words, it perpetuated

[1] *Arch. roum. path. expér. et microb.* **7** (2): 135, June 1934.

itself from year to year under the normal local conditions of anophelism and humanity. The next year Barber and I uncovered similar situations in Russia, and here and there other examples have been cropping up of so-called harmless races caught in the act of propagating malaria. This can only mean that anophelines, normally cattle-feeders, will under certain circumstances resort frequently and in considerable numbers to man.

While the attachment of a free living parasite like the mosquito to a particular host is never obligatory but always more or less facultative, so that there is nothing hard and fast about such a relationship, it is of the greatest importance for disease control to find out if possible the factors which can induce anophelines in large numbers to desert their habitual victims in favour of man. We think at once of the fleas which have their preferred hosts, but easily spread under certain circumstances to other host species. There are many kinds of flea: *Pulex irritans*, the well-known bedfellow of man, dog and cat fleas, and fleas of rodents—squirrels, rats, &c.—of special interest to us because they spread plague among these animals. Like mosquitoes, they are not rigidly specific in their feeding habits, and this makes them dangerous. When there is an epidemic of plague among the rats and a great many of them die, the fleas commonly turn to man for nourishment, and we begin to have cases of human plague. The insufficiency of one host drives blood-sucking insects to another.

If this is true of fleas, why not also of mosquitoes? Cragg thought epidemics of malaria in India might be in part a consequence of the dying off of a large portion of the cattle in prolonged periods of drought. The maintenance of an animal barrier to protect man from malaria was suggested years ago in Italy and has had various applications in many countries. There are those who would put almost their whole reliance on such measures, from Falleroni,[1] who

[1] *Riv. Malariol.* **8** (3): 315, May–June; and (5): 590, Sept.–Oct. 1929.

believes that an intelligently subsidized animal husbandry with scientifically constructed and properly located pigsties and stables would do away with malaria entirely, to the enthusiast who advocates a pig under every bed as a substitute for a mosquito-net. Just as plenty of rats reduce the probability of human plague, so plenty of cows, horses, and pigs would, according to the 'zooprophylactic' school, mean the virtual cessation of malaria transmission.

Schüffner and Walch,[1] I think, first demonstrated the fallacy of such reasoning. They had observed in Central Sumatra that stabled water-buffalo were many times as attractive to *A. sinensis* as man, and when they were confronted with a *sinensis*-borne malaria on the east coast of Sumatra, where the buffaloes were not housed at night, they had a number of protective stables built. To their surprise these did not have the slightest influence on the malaria situation. The anophelines continued to bite the men in their barracks to the same extent as the buffaloes. Returning to the problem ten years later, Walch,[2] now armed with the precipitin blood test, showed that unlike the *sinensis* elsewhere, the Sumatra form is but slightly attracted to animals. With few animals about, 90 per cent. of the *sinensis* caught in houses contained human blood, but if there were many animals this was reduced to 83 per cent. With a cattle-feeder like *maculatus*, however, the presence of animals brought the percentage down from 97 to 11 per cent.

Animal barriers then are sometimes effective in reducing malaria and sometimes not, according to the kinds of anopheles present. It is meaningless to inquire how many domestic animals will constitute an effective barrier until we know the various degrees to which the local anopheline species are amenable to animal attraction. In the case of *maculipennis* it has been observed for over thirty years that wherever domestic animals are stabled at all, every race and

[1] *Meded. Burg. Geneesk. Dienst. Ned.-Ind.*, N° 1: 2, 1921.
[2] Rev. by *Trop. Dis. Bull.* **31** (3): 158, Mar. 1934.

variety is attracted in greater numbers to animal quarters than to those of man. This has been called deviation by animals, but if Marchoux is right in thinking that *maculipennis* has always been a parasite of domestic animals, as would seem likely from its present habits, it would be more logical to say that under certain circumstances it is man who occasionally 'deviates' the mosquito from animals. Throughout northern Europe, and over large areas in southern Europe as well, virtually all the *maculipennis* live at the expense of domestic animals, and invasion of human habitations is irregular and in small numbers. But the amount and the effectiveness of the deviation vary from place to place. It is never complete, and numbers of anophelines filter into houses under all sorts of conditions, and bite people instead of animals. There are few hard and fast rules in biology, and such differences in biological characters must be expressed in terms of degree. We know that *typicus*, *melanoon*, and *messeae* are deviated by stabled animals to a far greater extent than *elutus* or *labranchiae*, and that *atroparvus* comes somewhere between. We do not yet know of any region in which *elutus* or *labranchiae* are not associated with an intense malaria. These two forms, so much alike in instinct and physiology, persistently try to enter bedrooms even in the presence of an abundance of animal blood. They wander back and forth between house and stable biting man and cattle indifferently. Under such circumstances animals cannot be said to deviate the anophelines so much as to dilute the blood-supply, adding to the host population a quantity of unsusceptible individuals which serve to nullify a considerable percentage of infective bites.

Given certain races, however, with distinct food preferences, we can now raise the quantitative question once more. How many cows, horses, and pigs *per capita* of population will be required to deviate *messeae* or *atroparvus* effectively? Theoretically there should be a point at which

the mass attraction of the larger domestic animals for certain anophelines will keep them from attacking man in such numbers as to bring about the transmission of malaria. Barber and Rice[1] made a census of the animals in some villages of Greek Macedonia where they were working, and for every hundred persons there were within village limits at night 44 horses and donkeys, 120 head of cattle or buffalo, 6 pigs, and at least 22 sheep and goats. This was not enough to keep *messeae* and *typicus* out of the houses altogether, for about 6 per cent. were found with human blood, but it rendered them harmless by preventing them from transmitting malaria.

Deviation then may be anything but complete and still be effective. This is due to the highly complex nature of malaria transmission, and the obstacles in the way of its successful accomplishment. The mosquito must first bite a person who is in condition to infect it, which surprisingly enough turns out to be a rather unusual coincidence. 'It is relatively difficult', wrote Grassi, 'to find a malaria case capable of infecting anophelines.' Only a very restricted group of malaria parasites—the sexual forms or gametocytes—can infect mosquitoes, and they appear only fitfully in the circulating blood, coming without warning and as suddenly disappearing for long periods without apparent reason. They have no tendency, as have some parasites, to appear with greater frequency in the special hours when the insect carriers are actively biting. The more chronic the case the scarcer they are, so that we may have to examine hundreds of individuals in a population steeped in malaria to find one with the right number and quality of gametocytes to infect a mosquito. Students of malaria will recall Barber's[2] strenuous efforts to find a certain number of 'good infectors' in Panama for an important experiment.

'The conditions of our experiments', he writes, 'demanded that

[1] *Am. Jl. Hyg.* **22** (3): 512, Nov. 1935.
[2] *U.S. Pub. Hlth. Repts.* **44** (24): 1409, 24 June 1929.

the patient have sufficient gametocytes in the blood to infect mosquitoes at a single feeding and we had much difficulty in getting enough patients suitable for our experiments. In all we examined over 1,500 blood specimens and found over 400 with parasites in the peripheral blood. Among these positives we found a considerable number with very few gametocytes but only twelve with sufficiently heavy infections to afford good "prospects". . . . In five [of these] the preliminary feedings gave negative results and the cases could not be used.'

Clark thinks that this business of being a consistent infector of mosquitoes is a family trait, and that a certain few individuals, lacking possibly in resistance, keep malaria going in a community. At any rate, if the anophelines are sufficiently numerous and persistent, some of them will get infected.

The mosquito must now mature the infective elements in its own body before passing them on. The sexual forms mate in its stomach, and in about two weeks under favourable conditions the daughter parasites (sporozoites) invade its salivary glands and are ready to be set free in the bloodstream of another human being. The time required, however, depends on the external temperature. Under 16° C. (about 60° F.) the sexual reproduction of the malaria parasite is brought to a standstill in the body of the mosquito, and as summer temperatures in northern Europe often approach the minimum necessary for this so-called 'extrinsic' cycle of development, progress may be slow and intermittent. But any undue delay will greatly affect the chances of malaria transmission, for the length of life of the average anopheline is at its shortest in summer. The mortality among them, as nearly as we can calculate from the descending curves of density after a sudden suppression of breeding, is more than 50 per cent. a week. Theoretically only one in four will live long enough to transmit malaria, and, as a matter of fact, in some experiments of De Buck and Swellengrebel[1] with large numbers of infected anophelines under more or less natural conditions, only 15 per cent.

[1] *Meditz. Paras.* **4** (1–2): 29, 1935.

survived as long as four weeks between April and October. These authors[1] believe indeed (and they are supported by some laboratory observations of James) that in northern Europe, during spring and early summer, the sexually active female, occupied intensively with reproduction and forced to lay huge batches of eggs at short intervals, is exposed so frequently to mortal hazards that she almost never survives to mature a malaria infection. It is this, they think, rather than an overmastering attraction toward domestic animals, that keeps *atroparvus* from becoming a malaria vector in Holland in the summer time.

However, let us suppose that a long-lived insect happens to meet a good infector in its youth and is ready to make an infective bite. It may, of course, have outlived its infection if, like *atroparvus*, it manages in autumn to survive to a good old age. The malaria germs degenerate and die in its salivary glands in six or seven weeks, *falciparum* more quickly than *vivax*.[2] This sharply limits the period of transmission and prevents infections from being carried over the winter in the mosquito. But if the bite is really infective, it may be wasted on a person already infected with malaria, or on a cow or a pig. Here is where the chances against successful transmission mount rapidly. Barber and Rice collected fifty-four infected *elutus* of which they were able to determine the source of the last blood-meal. Sixty-three per cent. had bitten some domestic animal, and yet of all the varieties *elutus* is the one which bites man most freely. The most astonishing thing about malaria, considering the chances against its successful transmission in nature, is the appalling amount of it in the world. This can only be explained by the enormous number of man-loving anophelines. Nature, as always, succeeds in achieving its ends through the prodigality of

[1] *Quart. Bull Hlth. Org. L.o.N.* **5** (2): 295, June 1936.

[2] Boyd, M. F., Stratman-Thomas, W. K., and Kitchen, S. F., *Am. Jl. Trop. Med.* **16** (2): 157, Mar. 1936.

its means, and this is the encouraging aspect of malaria prevention. A continuity and regularity of house visits on the part of considerable numbers of insects are necessary to spread and maintain malaria.

This becomes difficult or impossible for three or four of the races in the face of a 'stabular attraction' of a certain strength. In the Tuscan village of Massarosa the *maculipennis* population is more than half *melanoon*, the rest being *messeae* and *typicus*, and altogether 1 in 400 has been found with human blood. The chances then would be 1 in 160,000 that any individual mosquito would bite two different human beings, and 1 in 640,000 that it would bite the second person two weeks after the first. There is no malaria in Massarosa, but if a malarious visitor in condition to infect mosquitoes should put up for a night at an isolated farm with a family of six or eight members, it would require about four and a half million of the local *maculipennis* all converging upon that farm to ensure transmission of the infection. Since only two or three thousand are ever found resting in the daytime about such a centre, the margin of protection against malaria must be very broad.

It is not only number of animals which counts, but quality and condition also. Horses are less attractive to certain races than cows or pigs, and since *maculipennis* bites more willingly indoors, animals which are allowed to graze all night are always less effective than those which are stabled. Nor is it a static situation, for it depends on a sort of balance between anophelines and food supply, and while the number of domestic animals does not change materially from year to year, the production of mosquitoes goes up and down through an extraordinary range. In a favourable breeding season anophelines may overflow from the stables into the bedrooms through sheer force of numbers.

The quantity of mosquitoes which can be tolerated in bedrooms without danger to the public health is also a relative matter. It depends naturally on whether there are

sources of infection available in the form of human malaria carriers. A defence mechanism quite sufficient under normal conditions might be broken down by an unusual or continual arrival of gametocyte carriers from the outside. I remember that while the park system of Boston, Massachusetts, was being constructed by Italian labour in 1906, an extraordinary epidemic characterized by intermittent fever broke out in a residential district known as Back Bay. This was eventually diagnosed as malaria, to the general astonishment, since no one was prepared for such a peregrine visitor. The introduction of an infected labour force, together with some possible increase in anopheline production during the transformation of the land, had upset a balance which was protecting the population. In the same way a constant stream of malaria convalescents to a health resort might lead to some local spread of the infection.

Where malaria maintains itself with difficulty, the gametocyte factor has a peculiar importance, as shown by the extraordinary situation uncovered by Swellengrebel in North Holland. In a certain small village there was a curious focal distribution of malaria which was limited to a few families where most of the enlarged spleens and infected mosquitoes were found, and these were always families with a large number of small children. In fact, families with no children, or only one or two, rarely had malaria. It is not inconceivable that malaria might die out in such a community if there were a lower birth-rate.

Barber and Rice in West Africa made a somewhat similar observation. In the labour camps of certain rubber estates in Liberia, where there were practically no women or children, the anopheles were so numerous that the intensity of malaria was very high. But in Nigerian villages with much reduced anophelism, these authors found equally high malaria indices. The presence of many small children compensated for a relative paucity of anopheles.

Thus the three factors we have been discussing—the

numbers of anophelines, the attraction exerted upon them by the domestic animals, and the presence of infective people —are always acting quantitatively and independently to influence the amount of malaria transmission. The stability of the resultant balance will depend on the extent to which they are variable. How they may all work together to demolish the biological defences of a population threatened by a relatively harmless anopheline is illustrated in the recent malaria history of Mantua, a city built in ages past for military security in the midst of marshes and lakes, which breed only fresh-water varieties. Since the marshes lie between the city and its farm lands, its animal barrier consists mainly of its livery stables, and with this dearth of live stock is associated a prodigious anopheline production. Even so, malaria had fallen to a low point—about a hundred cases a year—in 1914, when there began an epidemic period reaching its peak in 1924 and subsequently declining. This rekindling of the infection was a consequence of the immigration of returning soldiers infected during the War. It brought a decade of disturbance to a long-standing biological equilibrium between anophelines, stabular attraction, and gametocyte carriers.

We are far from being satisfied with such a bald analysis of the more obvious quantitative factors which regulate the level of malaria transmission. We are dimly aware of an infinity of evanescent influences, qualitative and perhaps mainly physiological, which continually and profoundly affect the conduct of anopheles and their relations with man. These lend that aspect of inconsistency to the behaviour of the insects which is the despair of those who pretend to lay down rules of conduct for living beings. The effect is often to create apparent exceptions which tend to obscure sound generalizations of fundamental value.

On one occasion, long before anything was known of *maculipennis* varieties, Grassi,[1] the Italian biologist, spent the

[1] *Atti R. Accad. Naz. Lincei., ser. 5 sem. 2*, **30** (2): 11 July 1921.

night in a peasant's house at Orti di Schito, at the lower end of the non-malarious valley of the Sarno not far from Pompeii. This is an area, formerly of marsh, now a series of slow-moving canals between truck-gardens, which produce innumerable anopheles. He was astounded to find that not one of these would bite either him or his assistant, Neri, or for that matter any of the local inhabitants, though the houses were old and rather damp. He slept there several times with the same result, and with prophetic insight wrote, 'One may conclude that the anopheles of the Orti di Schito form a biological race which does not bite man.' (We now know that Orti di Schito breeds a pure strain of *typicus*, for we have never found a single specimen of any other race after many years of observation.) Anxious to test his theory in other regions of anophelism without malaria, Grassi[1] and Neri (who served as eyes, arms, and legs for him in his old age) went to Massarosa, a Tuscan village in which Celli had made a great many observations and had even noted the indisposition of the local anophelines to attack man. Here, however, installed in the little inn with its clean white bedrooms and surrounding stables full of pigs, horses, and cows, he was visited by a veritable swarm of *maculipennis* which entered during the night and of which he captured about three hundred. Grassi was puzzled by this all the rest of his life, and could never see his way clear to identify the 'factor *x*' of anophelism without malaria, with a cleavage of *maculipennis* into races. We have tried to repeat Grassi's experience on several occasions, but we have never seen the anophelines (all obligate fresh-water breeders) enter the bedrooms, nor was Van Thiel[2] more successful on a visit to Italy. He, with the same assistant Neri, slept in the same rooms, both at Schito and Massarosa, where Grassi had spent the night, and has reported that no anophelines entered and no *maculipennis* with blood was found in the

[1] *Riv. di Biol.* **3** (4): 421, July–Aug. 1921.
[2] *Riv. Malariol.* **12** (2): 281, Mar.–April 1933.

morning. These sudden invasions of houses by the so-called innocuous races are exceptional, but they occur from time to time, as Martini himself observed on an island in the lake of Schwerin, which has never been known to produce anything but *messeae*. On one night he was severely bitten by more than sixty *maculipennis*, which seems to show that there are circumstances under which *messeae*, and probably also *typicus* and *melanoon*, will eagerly bite man, even though the conditions may be fulfilled only on particular occasions in areas where deviation by animals is usually completely effective. Martini noted that the weather was windy and threatening on the night when he was bitten, and I too have been attacked by fresh-water *maculipennis* in a peasant's cottage during a thunderstorm. At all events, the determining influence is casual and fleeting, and the houses into which anopheles will enter *en masse* on occasional nights in summer are ordinarily completely ignored. Furthermore, such invasions apparently are never the cause of malaria, being sporadic and infrequent. They remind one rather of the annoying irruption of the biting stable-fly *Stomoxys calcitrans* into houses under depressing weather conditions. One thing is certain, the phenomenon is linked with the conditions of a particular night and not those of a particular house.

There is something more individual and mysterious in the stimuli which constantly lead *atroparvus* into human habitations in certain well-defined but extraordinarily dissimilar areas of its wide range. By all tests, *atroparvus* is one of the 'zoophilic' races, easily deviated by animals of all kinds. In France, in Italy, and in all but a small corner of Germany, although it occurs in great numbers, it is usually harmless. Nevertheless, it is the cause of practically all the malaria of Europe north of the Alps, and of that of Spain and Portugal as well. Moreover, in Holland and Germany it manages to keep up a low grade of endemic malaria in just those districts (North Holland and East Friesland)

where cattle-raising is the principal industry of the inhabitants. And to complicate the puzzle still more, in the contiguous areas to the east and west, with much the same

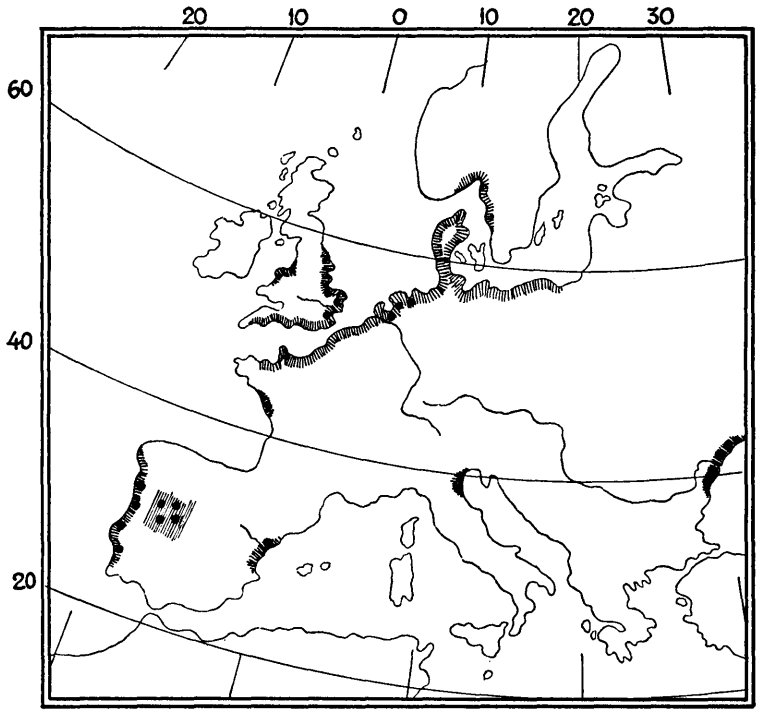


FIG. 6. MALARIA IN THE RANGE OF *ATROPARVUS*.

kind of people and industries, the same mosquito causes no malaria at all. So within the broad field of 'anophelism without malaria' we have (as Martini has remarked) a problem of '*atroparvism* without malaria'.

The Dutch observers, Korteweg, Swellengrebel, and others, have called attention to the fact that the malaria of Holland has some peculiar characteristics, and one of them is that it reaches its maximum very early in the year, in

May or June, before the anophelines begin to breed in numbers. They argue that it must be due to the mosquitoes of the year before, the infection remaining latent until spring. They have found out that while *atroparvus* and *messeae* are much alike in their preference for the stables in summer, they behave very differently as winter comes on. *Messeae* retires from egg-production in the autumn and begins to lay on fat for the winter. Martini[1] has noted that before the end of September it migrates as a rule to higher places and goes into solid hibernation in cold, unoccupied shelters. *Atroparvus*, on the other hand, becomes restless some time in August and moves about uneasily from one part of the stable to another. It seems to have only a rudimentary instinct which tells it to prepare for winter, like that which causes a hen to rush about in the spring with a straw in its beak, indulging in some vague idea of building a nest. Nothing comes of it however. Nature kindly shuts off egg-production, and *atroparvus*, in a state of 'gonotrophic dissociation', settles down to winter in a warm stable with plenty of available food. If, as often happens, it takes up winter quarters in a house, it lives upon the family; and if the mosquito should be infected or some one in the house should be a carrier, by spring most of the family will have contracted malaria and will have passed it on to the rest of the anophelines sheltering in the house. The malaria will thus have a very focal distribution. In a recent report (1934) to the Rockefeller Foundation Swellengrebel describes the conditions in a double house under the same roof: in one half there were ten people with five malaria carriers, and 441 *atroparvus* of which 107 were infected; in the other half there had been no malaria in the family in 1934 and of 301 *atroparvus* only three were infected.

Here is undoubtedly the true explanation of so-called 'malaria houses' on the English coast which attracted the attention of James in 1916. It is not the special attraction

[1] *Riv. Malariol.* **11** (6): 753, Nov.–Dec. 1932.

of a few dark, damp, and unventilated houses which bring anophelines indoors and create malaria foci. Nothing like this happens in inland places where *messeae* prevails. The presence of malaria is due to the occurrence of a semi-hibernating race of anopheles and not to good or bad housing or the standards of living of the people.[1] (Fig. 7.) That there may be under these conditions some houses with more malaria than others is not to be doubted. Swellengrebel[1] has made a very careful study of anophelism and malaria in Uitgeest, a little village of North Holland. He found that 68 houses harboured virtually all the infected anopheles. They averaged 20 per house and all were *atroparvus*. The other 133 houses contained only uninfected mosquitoes. Thus two-thirds of the families knew only by hearsay that there was malaria in the village, while the other third revealed an almost tropical incidence with a high spleen rate. The malarious families did not live in any one section but were distributed evenly throughout the village, and, in casting about for an explanation of this focal character of the disease, he discovered that they were the families with the most children. 'Malaria houses' could infallibly be detected in this way, and, as a measure of economy in the subsequent campaign to eradicate infected mosquitoes, only those houses were selected for disinfestation where there were more than four children under 16. Such houses contained more anophelines, too, and malaria was conserved in the family like lice in a bird's nest, the *atroparvus* acting for a couple of months each autumn as a medium of domestic exchange, while the parasite contrived during the rest of the year to survive in the human hosts. It was found that a house could remain a focus of infection for two consecutive autumns without open cases, the gap being bridged by 'apparently healthy carriers'.

This interesting explanation of the relationship of *atroparvus* to malaria in Holland and England does not,

[1] *Quart. Bull. Hlth. Org. L.o.N.* **5** (2): 295, June 1936.

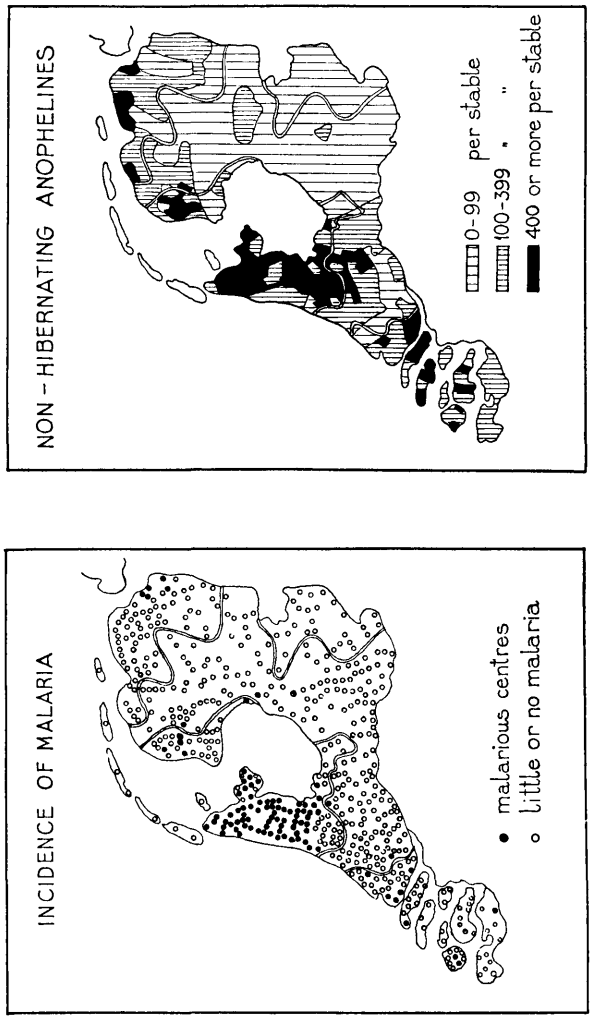


FIG. 7. RELATION OF *ATROPARVUS* TO MALARIA IN HOLLAND. (*After* Swellengrebel)

however, serve to clear up the general mystery involving this race. *Atroparvus* does not cause malaria wherever it occurs, and in many places, as in Spain and Portugal, it is certainly a summer and not a winter carrier. It enters houses and bites man in its active and reproductive season, and the malaria epidemic soon follows in the same year.

Neither does the long latency of the malaria in northern Europe as a whole seem to depend on winter infections and a semi-hibernating anopheline. In central Russia, for instance, an early spring peak and an autumn decline in the malaria curve is the rule. Here are the monthly averages for twenty-five years of the malaria cases treated in the dispensary at Gorki (formerly Nishni Novgorod):

Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
154	173	307	453	**600**	500	403	361	265	275	183	145

The peak is in May, as in Holland, yet no *atroparvus* has been found in the entire region, all the local races going into complete hibernation. The first adults are seen in mid-April, the first eggs in May; the maximum production is in July or early August, and hibernation begins about 20 August, after which there is no further transmission.

But even in northern Germany, in *atroparvus* regions, summer infections doubtless occur and remain latent until the next year. Weyer,[1] of our laboratory in Emden, writes that *atroparvus* is found in bedrooms mostly in the warm summer months, seldom in autumn, and practically never in winter. Martini[2] has unearthed accounts of the movements of troops in Germany during the last century which lend support to this view. In one case, among soldiers moved in the spring from a non-malarious zone in central Germany to Kiel and sent home again before the end of the summer, the majority showed the first signs of malaria in the following spring. I have already mentioned the infection experiment carried out by Schüffner on himself and

[1] *Arch. f. Schiffs- u. Trop.-Hyg.* **38** (3): 131, Mar. 1934.
[2] Ibid. **38** (1): 43, Jan. 1934.

other volunteers. The interval of eight to ten months between inoculation and first attack suggests that in Holland also primary attacks in April and May might be the result of natural infections as early as July or August. Van Thiel in a recent article on Dutch malaria has come to a similar point of view, admitting the possibility that both summer and autumn infections in Holland may be carried over into the next year.

Atroparvus then does continually get into houses in the summer under conditions which bind races like *messeae* and *typicus* to the stables. In France, Italy, and on the Baltic Sea, it does not enter in sufficient numbers to be a vector of malaria; in England, Holland, and the North Sea coast of Germany it is the agent of a mild infection which indicates a constant infiltration, while in Spain and Portugal it brings about a malaria situation of public health importance. In none of these regions can we eliminate all of the factors which we have already discussed as tending to break down the efficiency of an animal barrier and to precipitate a zoophilic mosquito upon man, a less acceptable host. Swellengrebel has found that *atroparvus* is no more susceptible to malaria than *messeae*, and that if anything it yields to stabular attraction even more easily than the other races in the malarious districts of Holland. He does not believe there is a greater density of *atroparvus* in the malarious than in the non-malarious areas, and, since we have to do with a long-established endemic situation, the parasites are of an indigenous strain and the spread of infection does not depend on the constant immigration of gametocyte carriers from abroad. He thinks therefore that the winter behaviour of *atroparvus*, or more particularly the separation of its nutritive from its reproductive functions during a certain period, is the principal if not the only cause of malaria in Holland. In north-west Germany the numbers of *atroparvus* are the striking thing; in England James feels that the importation of foreign gametocytes plays a significant role, and in Spain

the possibility of an inadequate animal barrier cannot be rejected. However, it is worth noting that in the rice-fields of Spain near Valencia, where *melanoon* is produced in great numbers, there is no malaria, while in the rice-fields of Portugal near Lisbon, where *atroparvus* prevails, malaria is a serious problem. The difference is in the mosquitoes rather than in the conditions.

The feeling is forced upon us that *atroparvus* is not so firmly bound as the fresh-water forms to the narrow range of hosts or microclimatic conditions found in stables. Slight variations in the complex circumstances of its environment, which have so far eluded our search, seem able to raise or lower the biological threshold which protects the homes from invasion by this race. Martini and Teubner[1] of Hamburg have begun to explore the little-known realm of anopheline physiology and sensibility to microclimatic influences. There are significant differences between *messeae* and *atroparvus* in their reactions to their surroundings. These might be quite enough under certain borderline conditions to make a carrier of one species and render the other harmless.

A. maculipennis is a domestic mosquito, which means that it will enter any man-made structure without hesitation, and, in fact, almost all of its fundamental instincts—for nourishment, for protection from the light and weather, for egg-ripening, and for hibernation—cause it to take shelter somewhere. Only the necessities of procreation and oviposition, and at times the impulse to invade new territories, take it out of doors. Most of its life is spent under a roof. The physical conditions of temperature, humidity, light, ventilation, &c., which constitute the so-called microclimate of its habitual shelters, are therefore of the greatest importance to it. It would seem that there must be a particular sort of microclimate adapted to each of its various needs. Thus, while it is hardening its tissues and gaining strength upon

[1] *Beih. Arch. f. Schiffs- u. Trop.-Hyg.* **37** (1): 1, 1933.

emergence from the pupal case, it will require and probably seek one set of conditions; for the digestion of blood and the ripening of eggs another, and for hibernation a different set altogether. It may be that in oviposition it is guided to the favourable breeding-places of its own race by the microclimate, which we may suppose lies stratified just above the surface of the water. If this is true—and it is in the insect tribe especially that the most complicated activities prove to be inherited reflexes to environmental stimuli—it would not be strange if the biting reflex were also to some degree responsive to a similar set of external circumstances. In critical situations this might turn the scale in favour of one host or another, but it cannot be the essential determinant in choice of hosts. For if hungry anophelines were all very much alike and were attracted to houses or stables, as the case might be, by certain physical conditions prevailing in them, malaria would depend principally on the way man keeps himself and his domestic animals, and very little on the prevalence of this or that species or race. Our experience tells us decisively that this is not so.

It has been difficult to write briefly about a subject of which we know so little.[1] We can sum it up, however, in a few words. Each race behaves according to its peculiar instincts and adaptations, for in biological individuality and genetic isolation it is not essentially different from a species. The individual mosquitoes are undoubtedly influenced by microclimate in all their physiological activities, and the biting instinct is also guided, modified, or restrained by the physical conditions of the environment, but in a different way and to a different degree for each race. *Elutus* for example seems relatively insensible to such influences. It will rest in comfort just beneath an iron roof on a blazing midsummer day, and at night it is wide-ranging and indiscriminate in its search for food. *Messeae*, on the other hand,

[1] For a general discussion of the race question consult Martini, E., *Arch. f. Schiffs- u. Trop.-Hyg.* **35** (12): 707, Dec. 1931.

prefers cool, damp, and dark places after sunrise, and in biting is narrowly limited to certain hosts. But while behaviour is always a resultant of the independent forces arising respectively from instinct and environment, instinct seems usually to dominate in questions of food. The net result is that two of the races preserve a wide faculty of choice as to host, while all the rest limit themselves to domestic animals *unless certain disturbing factors intervene*. Some of these factors compel the insects through sheer necessity to attack a less preferred host, such as man, and they act equally upon all the races. Such factors are the dearth of animals or a great increase in the numbers of the mosquitoes themselves. There are also conditions which merely increase the danger of the casual normal contacts with man, such as the presence of an unusual number of infective persons, or some special susceptibility to malaria on the part of certain mosquitoes (a condition which does not seem to exist in *maculipennis*, but may be very important in the case of *superpictus*). Finally, there are those obscure stimuli which here and there seem to exert a strong positive attraction upon mosquitoes, drawing them constantly or at odd times into places commonly unattractive to the race, and making malaria carriers out of ordinarily harmless forms. For want of better knowledge we ascribe these stimuli to an indefinite complex of physical conditions known as microclimate, by which we attempt to explain apparently erratic behaviour on the part of anophelines not referable to any of the more tangible factors mentioned above. It may be the search for a particular microclimate which on the approach of winter sends *atroparvus* into warm houses but condemns *messeae* and *typicus* to frozen immobility in hay-lofts and belfries. It is microclimate, we suppose, which makes *atroparvus* a malaria carrier in some places, by weaning it from a natural fondness for animals which elsewhere is effective in breaking its contact with man.

Let us not complain if the explanation of 'anophelism

without malaria' which began boldly enough with a number of dogmatic assertions has now tailed off into surmise and not too well-founded speculation. As Alice said to the caterpillar in a similarly difficult situation, 'I'm afraid I can't explain it more clearly for I can't understand it myself, to begin with.' But what makes the subject highly interesting to malariologists everywhere is the growing conviction that there are similar problems to be solved in connexion with all the widespread species of anophelines. Take for example *A. ludlowi*, first described by Mrs. Ludlow in the Philippine Islands, where she found it breeding innocuously in fresh-water streams in the hills. Christophers ran across it in the Andaman Islands breeding in salt water and causing a terrific amount of malaria. It turned out to be the most formidable vector in the Dutch East Indies, breeding in Java in straight sea-water in the fish-ponds along the coast, but in Sumatra in foot-hill streams thirty miles or more from the ocean. Yet when Walch banished it from the fish-ponds of Java, in the way later to be described, it proved to be incapable of adapting itself to the fresh-water streams and marshes which were present in abundance, and its numbers fell at once to insignificance. Its existence was dependent in Java on water of a definite salinity. Such fish-ponds were also to be found in the Philippines, and these turned out to be breeding *ludlowi* too, but nothing was done about it, because this *ludlowi* was not engaged in the transmission of malaria. This species-complex is now divided provisionally into four groups: *A. ludlowi* (type), a fresh-water breeder and non-vector in the Philippines and elsewhere; *A. ludlowi litoralis*, a salt-water breeder also a non-vector; and *A. ludlowi sundaicus*, which has both a fresh- and a salt-water form, both of which are vectors of malaria. Not a few of the other species present suspicious behavioural inconsistencies. *Hyrcanus*, *maculatus*, and *pseudopunctipennis* are carriers in one place and not in another. *Gambiae* and *funestus*

breed under quite dissimilar conditions in different parts of Africa. Here is a very important field of study. But it is not to be supposed that nature has been kind enough to help us distinguish the races everywhere by painting their eggs different colours. The attack must be from the physiological side. As Celli predicted, twenty years before anything was known about the races, 'These are problems on the threshold of the most abstruse biology, and hence no wonder our studies have not yet brought complete light. All the more reason', he adds, 'why we should not be too unilaterally theoretical or dogmatically restricted in any programme for the control of an epidemic rooted in time immemorial.'

FIG. 8. ANOPHELISM WITHOUT MALARIA: ITALY
The marshes behind Viareggio, the Italian summer resort

FIG. 9. ANOPHELISM WITHOUT MALARIA: SPAIN
Rice-fields hemming in a healthy suburb of Valencia. In both places, an intense production of *A. maculipennis*

IV

THE MAP OF MALARIA

Just as other natural things have degrees in respect to their properties and faculties, so also marshes, comparing one with another and in their relationship to man, may be more dangerous or less dangerous or hardly dangerous at all.

LANCISI: *De Noxiis Paludum Effluviis*, Bk. I, Pt. 1, ch. 5 (1716).

IT has taken the world a long time to ferret out the real agents of malaria infection. Each new discovery, instead of unmasking more culprits, as in the case of yellow fever, has been progressively narrowing the field for forty years. After centuries in which marshes were under the gravest suspicion, embedding in our language such fossil terms as 'malaria' and 'paludism', Ross succeeded in shifting the blame to mosquitoes. But Grassi[1] soon absolved them all except a single genus, the *Anopheles*, and in the flush of victory he announced that the anopheles mosquito was the 'clue to malaria'. Stephens and Christophers,[2] however, after a good deal of careful work, proved that in India, at least, a great many anopheles have nothing to do with malaria. In fact there are 150 different species of anopheles in the world, but only a few—hardly 10 per cent.—are efficient carriers, able without help to keep malaria going in a community. Each species, as we are now finding out, may be made up of any number of clans differing to such an extent that they will have nothing to do with one another. More than half of these are quite harmless, the others being black sheep with roving habits and catholic tastes that make them public enemies. Even these latter—*atroparvus*, for example—are not always harmful by any means, but only in certain places or under certain circumstances, for reasons we hope some day to find out and use to our advantage. And finally, among the very best malaria carriers the susceptibility

[1] *Atti R. Accad. Naz. Lincei*, ser. 5, **7** (7), 1898.
[2] *Reports to Mal. Committee Roy. Soc.*, ser. 6 (3), 1902.

of individual mosquitoes varies enormously. No small number are completely refractory to infection, and the percentage may well be on the increase if, as Huff[1] has shown in *culex*, susceptibility is an inherited character and behaves as a simple Mendelian recessive. The upshot is that in all the great family of mosquitoes, the really dangerous varieties found to be distributing plasmodia can almost be counted on the fingers.

The great amount of malaria in the world, then, is linked in each rural community with the presence of a mosquito which has decidedly exceptional habits for an anopheline. Two of the seven anophelines of Europe are in this class (a very large proportion as compared with other continents), but in compensation one of the two, *superpictus*, whose range touches only the south-eastern corner of Europe, is neither very numerous nor always very dangerous as carrier species go, and the *maculipennis* group, as we must now call it, is very much divided. Only three of the races are continual and obstinate carriers, the others being parasites of domestic animals, forced occasionally upon man by local circumstances. The result is, there are two kinds of malaria in Europe: one due to the presence of anopheline species or races which are habitual feeders on man and dangerous, therefore, in strict proportion to their numbers; the other due to local conditions, social or environmental, which permit a degree of contact between cattle-biting anopheles and man normally suppressed in an agricultural community through natural biological influences. There will be little relation between the numbers of such anopheles and the amount of malaria.

Now it is clear that the outlook as to the course of malaria in these two situations will be quite different. In the first case, anopheles enter houses instinctively in search of blood under all conditions and regardless of domestic animals. This is the mark of dangerous species everywhere. For if

[1] *Am. Jl. Trop. Med.* **15** (4): 427, July 1935.

two hosts are equally acceptable and accessible, the prevalence of one will not protect the other except as chance determines the distribution of the insects. In Kenya, for example, as in all of central and southern Africa, the redoubtable vectors are *costalis* and *funestus*, of which Kauntze and Symes[1] remark that although cows are kept in huts day and night until they become almost blind and their leg muscles atrophy for want of use, the mosquitoes show no inclination to neglect the human inhabitants to feed on the cattle. The amount of malaria is directly dependent on the existence and importance of particular kinds of breeding-places producing these mosquitoes and little if at all on the prosperity or nutrition of the people, the type of housing, or the amount and condition of the live stock. There may be biological ways of interrupting transmission without reducing the numbers of such mosquitoes, but we have not yet discovered them. Our best defence is still direct mechanical intervention: the elimination of breeding-places and the mosquito-proofing of houses. Only *elutus* and *labranchiae* of the *maculipennis* group belong unquestionably to this class, although *atroparvus* in Spain and Portugal makes a strong bid for membership. In Holland also, and possibly in other parts of north Europe, the peculiar hibernating instincts of *atroparvus* turn it in August from cattle-biter to man-biter and make it, for a couple of months at least, a dangerous mosquito, though in a small way.

In the second case, the amount of malaria depends only slightly and indirectly on the numbers of anophelines produced locally, and mainly on the degree to which a natural protective barrier between anopheles and man is deficient or inoperative. Regions may be very much alike as regards anophelines and yet have every degree of malaria, from a few scattered cases to a considerable epidemic. Failure of the automatic controls to function is, as we have seen, due

[1] Kenya Med. Dep.: *Rec. Med. Res. Lab.* No. 5, 1933; also *Trop. Dis. Bull.* **31** (3): 155, Mar. 1934.

to any one of a variety of factors which can throw the local mechanism out of balance, but these are surface phenomena provoked as a rule by underlying social causes of great moment, slow to change or disappear. Such causes are war, insecurity and disaster, a primitive or unbalanced state of agriculture, or a pioneering stage of civilization in which the conquest of new areas is associated with miserable living conditions, an unrestricted production of anopheles, and a paucity of domestic animals. Malaria of this type is on the decline in western Europe, but we can easily imagine that the situations in which we still find it are reminiscent of the general state of things a century ago when malaria was rife in almost every part.

The World War, for example, rekindled malaria in many regions where it had not been known for generations. In Czechoslovakia not only the mild *vivax* but the exotic *falciparum* malaria made its appearance, indicating a high rate of transmission, stimulated by the disorganization of rural life and the return of infected soldiers. Automatically in the course of a few years it disappeared—first *falciparum* and then *vivax*—without any specific measures of prevention. We have no report on the types of anopheline in Czechoslovakia, but we can assume with small probability of error that they are the usual continental fresh-water forms, *messeae* and *typicus*, which have now gone back to animals as their preferred hosts. Holland offers a rare chance of evaluating the attractiveness of the well-stabled animal. On a newly occupied polder, with many more houses than stables, one in six of the local anopheles will be found in the houses; but in an old polder, in which the domestic animals are equal or superior in number to the human beings, the proportion is more likely to be of the order of one in four hundred.

In central Russia, throughout the Volga river basin from Moscow to Astrakhan, we find a more serious and unusual state of affairs: a moderate degree of endemic malaria supported by *messeae* and *typicus*. All that we know of these

varieties shows that under the rural conditions of the rest of Europe they are now generally harmless, even in the Balkans. We have come to the conclusion that they are harmless because of the quantity of the larger domestic animals now stabled in areas of intensive agriculture and a developed animal husbandry. From our observations in Russia and those of Martini and Zotta in Roumania, we get the distinct impression of a rural population backward in this respect. It is not unlikely that Russia, while making great strides toward the introduction of cattle and the adoption of modern agricultural methods, may still be in much the same condition as that which characterized the rest of Europe in the days when malaria was more common. Endemic malaria, while widespread in Russia, cannot be termed intense and consists entirely of *vivax* infections. The outlook is, therefore, for a progressive development of rural life toward that condition in which, through effective deviation, the anopheles may persist but the malaria will disappear.

From the malariological point of view the decisive change which has come to primitive forms of agriculture is the introduction of the rotation of crops. Every three years or so the fields are planted with legumes for the enrichment of the soil. This would mean a great excess of fodder crops unless the economic balance were restored by an increase in live stock, and thus animal husbandry develops as an economic necessity and stall-feeding substitutes natural pasturage. There is little grazing-land left in Italy, for example, except in the mountains, for pressure of population makes it uneconomical. This produces optimum conditions for the deviation of the zoophilic anopheles. Such a development is beginning to be effective in Poland, for instance, where conditions used to be much the same as those of Russia. Malaria has now practically disappeared owing to a more balanced agriculture and the presence of no other anopheles except *messeae* and *typicus*.

There is one social condition which is usually linked with intense malaria transmission, and this is the pioneering phase of land occupation and development. One of the best examples of this in Europe is the delta of the Ebro in Spain, now become famous by reason of the multiplicity of reports and international studies which have been made on it, together with other deltas. The Ebro delta, in short, was first a desert; it was then reclaimed not many years ago for the cultivation of rice on a large scale, at which time it became extremely malarious; and it is now a prosperous and growing community in which malaria is only sporadic and with each passing year steadily approaches the vanishing-point. By far the most illuminating analysis of this situation was made a year or so ago by Sinton,[1] and I recommend this document to the careful attention of all who are interested in the problem of the gradual regression of malaria before an advancing agricultural civilization. No one has ever put the facts so simply and clearly before.

Sinton points out that there are four stages in the reclamation and occupancy of new areas. The first is the transformation of the land when the swampy places are being brought under cultivation. There are many non-immunes in the labour aggregations, while infected immigrants bring new strains of parasites and acquire others. There is a shortage of accommodation, with overcrowding, which greatly facilitates the spread of infection. There is a local increase in mosquito production, resulting from a disturbance of the natural balance in the fauna and flora, and between the mosquitoes and their enemies, leading to a high inoculation-rate. There is increased severity of clinical symptoms with an associated increase in gametocytes, due to primary attacks, new strains, young sporozoites, lowered resistance, and multiple infections. There is an absence of facilities for treatment and nursing, and finally there are few or no domestic animals.

[1] *L.o.N. Hlth. Org. C.H./Mal./202*, 23 Mar. 1933.

In the second stage cultivation begins, but the conditions of living are still primitive. There is usually a floating population of seasonal workers in summer, badly protected and a source of infection to the stable population.

This population enters the third stage well established and with better standards of living. We find a rising prosperity, adequate medical assistance, a natural increase in population, fewer transients, and perhaps a beginning of screening.

In the Ebro delta we are witnessing the fourth and permanent phase: a scientific agriculture with rotation of crops, production of forage, and an increase in animal husbandry. Though the anophelism is still so intense as to be almost unbelievable, its contact with man is already slight. The situation is beginning to resemble that of Valencia, an old-established rice-growing area farther south, where the dominant anopheline is attracted to cattle, and malaria has completely disappeared.

Much has been made of the fact that the Ebro region is a delta, but I doubt whether there is a problem of 'delta malaria', so called, as a phenomenon by itself. Each delta constitutes an independent malaria problem with its own peculiar conditions, and the happy solution of most of these problems has turned on the type of anopheline which has eventually prevailed over the others. As a result of a more scientific agriculture the map of malaria in Europe is thus steadily contracting toward the limits set for it by the spread of the anophelines which we have defined as inherently dangerous. Beyond this there can be no further 'natural regression'.

This is in conflict with Roubaud's theory that under certain conditions the introduction of live stock will build up a race of anopheles with strong biting parts, thus changing dangerous malaria carriers into cattle feeders. We now know that races, like species, may differ in dental armature, some having more teeth than others, but these are differences

rooted in time immemorial, unaffected by actual environmental influences. All our records show that anophelines of the same kind, whether they are found in bedroom or stable, will have the same average number of teeth, which is known as the 'maxillary index'. *Atroparvus*, for example, might possibly be taken to represent a race in process of becoming 'differentiated' (in Roubaud's sense) into a confirmed cattle feeder, so easily does it slip back, under unknown influences, to its old association with man. Yet we get no hint of this situation in its dental equipment. Eliseo de Buen[1] dissected more than two thousand specimens of *atroparvus* obtained from a malarious zone in Spain, and found that the tooth count was always characteristic of the race, not of the animal attacked.

Roubaud's theory was based on observations which led him to believe that man-biting anophelines have on the whole fewer teeth than the cattle feeders. This is quite another thing. If true, the reasons would be likely to be of an inscrutable evolutionary character. There is no implication that dangerous races can be changed into non-vectors by any rapid means at our command. The lower dental averages of southern Europe led Martini at one time to suggest that number of teeth might be correlated with size of insect and hence with climate, since water temperature controls to a considerable degree the size of anophelines —the warmer the water, the smaller the insect. The discovery of the *maculipennis* races, in which he took an important part, caused him to change his opinion. He now believes that each race has its own dental mean and that the general correlation between latitude and maxillary index (which in detail presents so many exceptions) is due to the geographical distribution of these races, two of the southern forms having low averages. Whether the parallelism between number of teeth and intensity of malaria in Europe is mere coincidence remains to be seen. At least, it is certain that anophelines are not restrained from biting the domestic animals by inadequate dentition. The malaria carriers differ from the rest of the anophelines of Europe only in the *degree* to which they bite human beings. All without exception resort to cattle more frequently than to man.

[1] *Med. Pais. Cálid.* 8 (2): 73, Feb. 1935.

Before the discovery of the zoophilic races, there were, of course, besides Roubaud's ingenious contribution, numbers of vague and unsupported theories to account for the deflation of malaria in Europe. All were based on progressive changes, social or environmental, which accompanied the decrease in malaria, such as:

better houses and food,
more quinine,
fewer mosquitoes,
colder summers.

Whatever value we may now care to assign to these factors (and we cannot absolutely discard any of them), the last one remains, of course, as valid as when it was proposed. Climate reigns everywhere with its 'prodigious might', and a slight change might seriously handicap an insect species or suppress it altogether, in its ponderous way. But the effect of a small average decrease in temperature would act, as Martini says, more especially to restrain and baffle the malaria parasites which develop within temperature limits much narrower than those of their anopheline vectors. Since even *P. vivax* requires at least 16° C. (60° F.) to make any progress at all toward reproduction in the body of the mosquito, the summer temperatures of northern Europe must often extend this period interminably, and in fact they can descend for weeks at a time to a level which might abolish the extrinsic cycle of the parasite altogether by prolonging it beyond the normal life-span of the insect.

It is possible also to speculate on the distribution of *maculipennis* races in Europe a century ago, and whether this has been changed a great deal in recent times. The

races, like true species, depend for mass production on the presence of particular types of surface water adapted to their several breeding-requirements. No two species like exactly the same combination of features. There may be overlapping in borderline situations, and there are curious invasions of unsuitable waters by species both in times of adversity and of excessive prosperity; but in the absence of conditions typically favourable to the aquatic stages of a species, that species will be lacking or rare. Thus *A. plumbeus* is dependent on insulated collections of rain-water in hollow trees or spring-fed pools in the recesses of dark caves and *A. superpictus* on running hill-streams and the restricted summer flow of torrents in the open sun. We take advantage of this, where we can, to attack only the breeding-places of malaria carriers, effecting a considerable economy by leaving the rest alone. Every such programme of 'species sanitation' is based on the two premisses that some species of anopheles are more dangerous than others, and that they often breed in different types of water. It was Malcolm Watson at the very beginning of the century who, as a Government surgeon in the Federated Malay States, first turned these differences to practical account. The famous Reports to the Malaria Committee of the Royal Society were just beginning to appear, revealing the importance of species in the relationship of anophelines to malaria. Studying their breeding-habits, he directed his attack against the dangerous ones.

The same thing, of course, holds true of races. There are salt-water and fresh-water races, stream breeders and pond breeders, and there are many very subtle characters besides which go to make up the specific fitness of a bit of water surface. It used to be thought that anopheles would be driven to breed in unusual waters if their customary breeding-places were destroyed, and this has sometimes been put forward as an argument against species sanitation. It might be even more plausibly urged that, under pressure,

one race might easily adapt itself to conditions found suitable by another member of the same group, from which it was physically indistinguishable. This was one of the chances which Walch[1] took when he drove *A. sundaicus* from the salt-water fish-ponds of north Java. There was fresh water in abundance near by, and it was known that the same anopheline, to all appearances, was breeding in hill streams of Sumatra, far from the coast. Nevertheless, *sundaicus* was not able in Java to maintain itself in fresh water. Swellengrebel has observed the same thing in Holland with regard to *maculipennis* races. *Atroparvus* is not able to compete with *messeae* in fresh water in Holland. It will invade fresh water when present in great numbers, but it cannot maintain great numbers in fresh water. The presence of a few larvae outside specific breeding-places has no importance at all. The larval density of *atroparvus* in fresh water is less than 2 per cent. of that in brackish water.

Progressive changes in the conditions of rural life during a century or so would be apt then to affect the relative prevalence of the different races if at the same time they modified the characters of the breeding-places. Now the agricultural transformation of land, drainage and the introduction of irrigation, the addition of lime and fertilizers to the soil, and the development of animal husbandry will produce in the long run changes in surface water which might easily affect mosquito breeding. In the Pontine Marshes in the last few years Missiroli believes that there has been a gradual change in the type of anopheline caught in shelters. *Elutus* and *labranchiae*, the principal enemies of the farmer in southern Europe, have been slowly decreasing in relation to *messeae* and *melanoon*, and we are perhaps witnessing the progressive realization of a biological change which in the end may put the seal of permanency on the elimination of malaria from this and

[1] *Meded. Dienst. d. Volksgez. Ned.-Ind.* **19** (3): 400, 1930.

similar 'bonifications'. The best-known example of the substitution of one race by another over a period of years is furnished by the Netherlands, where land is being continually reclaimed from the sea. For ten years or so, on new-made fields or 'polders' the breeding-places retain enough salt to produce quantities of *atroparvus*, a carrier of malaria in North Holland. As irrigation sweetens the water, and as new polders at the growing edge of the land remove the older ones farther from the sea, *atroparvus* slowly disappears and *messeae* takes its place, leading to a progressive and in the end complete fading out of malaria.

Two gradual changes then have been taking place in Europe in fairly recent times—the diversion of several widespread races of *maculipennis* from man to animals, and the substitution of certain refractory races by races more easily diverted. The latter process has been far less complete than the former. The persistent foci of malaria mark the breeding-places of the dangerous anophelines, and it is somewhat surprising to find that the geographical distribution of malaria is virtually the same as it was sixty years ago when we began to have trustworthy reports of its incidence. The Second General Report of the Malaria Commission contains some interesting maps showing the malaria in England and Holland at two different epochs, and I show below a similar map of Italy (Fig. 10). Any of them can be used just as well to show the geographical distribution of the vector races of *A. maculipennis*, which was evidently the same then as now. *Maculipennis* is also found along the entire Pacific coast of the United States, although, characteristically enough, malaria occurs only in spots. While we know nothing about the races there, the following remark by G. P. Jones in his *Short History of Malaria in California* is of peculiar interest: 'The distribution of malaria at the present time [1931] although greatly reduced in volume is with one exception practically identical with its distribution during the years 1849–54.'

Climate determines the range of a species, and hydrographical conditions its distribution, so that malaria depends, one might say, on physical geography—*Klima und Boden* again, in a new sense, though we have ridiculed

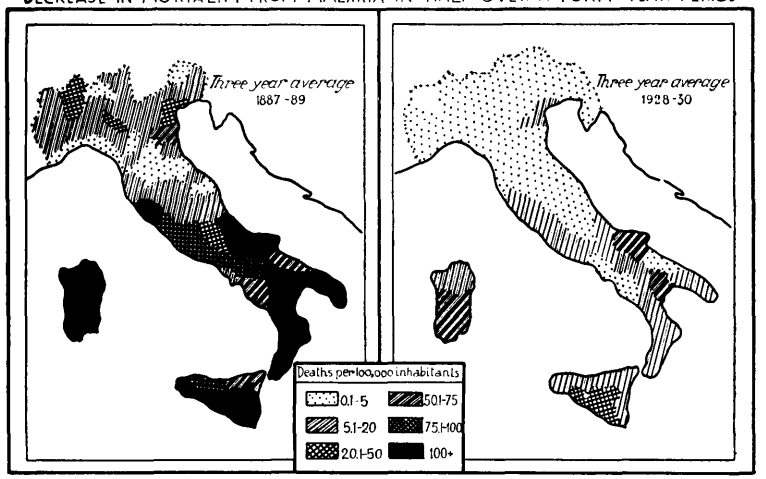


FIG. 10. While the deaths from malaria have decreased enormously, the distribution remains always the same—that of the man-biting anophelines, *labranchiae* and *elutus*.

them both as impostors in another connexion. Larval habitat, then, should absorb the attention of the malariologist in a very special way, yet 'while all of our knowledge of the epidemiology of malaria is rudimentary', says Boyd, 'the lacunae are nowhere more evident than in this phase of the subject'. I cannot hope, therefore, to present a simple and coherent account of the ecology of *maculipennis* larvae, for the more lucid I might succeed in making it appear, the more fallacious it would certainly be. But it may not be either futile or uninteresting to have a glimpse at a highly complicated subject in the process of being unravelled.

I should say the main division in *maculipennis* races is between those which breed only in fresh water, and those which can breed also in water of a certain salinity and are therefore more apt to be coastal forms. Why the

salt-resistant races are also the man-biters and malaria carriers of Europe is an interesting question. Perhaps they had less opportunity in fishing-villages to develop a host preference for live stock. It turns out that they are also more tolerant of heat. Possibly, as Martini suggests, they may have gained salt tolerance in a hot, dry climate through the need of extending a relatively limited breeding-area or through the evaporation and consequent hardening of the water in the pools, altering its density. With this increase in adaptability they could then invade northern saline waters which are unoccupied by other forms. There is little opportunity for competition between the salt-resistant forms, for their ranges touch but do not overlap; they divide among them the coast-lines of Europe. If any coastal region is not malarious it is usually due to the diversion of *atroparvus* to animals, for the other two forms, *elutus* and *labranchiae*, are always vectors.

The fresh-water breeders mingle in the same areas with each other and with the coastal forms, but each has a particular type of water which it prefers. We have come to this conclusion because, where only one type of breeding-place prevails over a broad area, we often find a race of *maculipennis* occurring in pure culture. In certain areas of Spain we find only *atroparvus*; around the fresh-water lakes of central Germany only *messeae*; in the foot-hills of the Caucasus only *typicus*. But really we know very little about the essential conditions which make a breeding-place attractive to a given race. One race will be found mainly in standing water and another in flowing water, but there are so many exceptions that we suppose it is not really movement of water that counts, but some associated character. Running water is apt to be cooler than standing water, and has a different flora and microscopic life. Temperature indeed seems to play a great role. Hecht showed that, given their choice under experimental conditions, *atroparvus* would choose warmer water than *messeae* for egg-laying.

One difficulty with this is that anophelines in nature lay their eggs at night. The water surface of some upland shallow marsh or pool may rapidly cool off at sunset and give no indication of its midday temperature to an egg-laden anopheline. A *subalpinus* place may be actually colder at night than a *typicus* place, reversing the daytime conditions. Shannon points out, however, that in quiet water depth has an important influence on temperature, especially its constancy, and depth is correlated with type of vegetation. The vegetation would indicate to the insect something of the character of the water, not only as to depth and daytime temperature, but as to salinity as well, just as a naturalist can tell without tasting whether a marsh is salt or fresh by a glance at the flora.

How far then is salinity in itself of importance to the mosquito? There is a very pretty correlation in Holland between the degree of salinity of the water and the prevalence of *atroparvus* larvae as worked out by Swellengrebel[1] and his colleagues from a great number of observations.

	Larval population	
Parts per 1,000 of Chlorine	*Per cent. of* atroparvus	*Per cent. of* messeae
0–0·1	10	90
0·1–0·3	25	75
0·3–0·5	31	69
0·5–0·75	50	50
0·75–1·0	67	33
1·0–1·5	82	18
1·5–2·0	91	9
2·0–3·0	95	5
3·0–4·0	97	3
4·0–8·0	98	2

In spite of such beautiful gradations of effect, it seems likely that salt has only an indirect influence on the inquiring mosquito, changing the nature of the breeding-place in a way more obvious to the insect than to us. For how can a mosquito determine differences in salt-content of the order

[1] *Quart. Bull. Hlth. Org. L.o.N.* 5 (2): 280, June 1936.

of one-tenth of a part per thousand? *Atroparvus*, which lays its eggs in brackish water north of the Alps, finds fresh water more to its liking in Spain (Fig. 11) and Italy. Perhaps it is not looking for salt at all but some other character which happens to be associated with salinity in northern Europe. We pay a great deal of attention to parts of NaCl per thousand in its breeding-places because salinity is measurable, but the mosquito itself may care nothing about it. It may be this is why, when put to the test in captivity, *atroparvus* lays its eggs indiscriminately in all the solutions we set out for it. A dish of salt solution in the laboratory can bear little resemblance to the intricate balance of flora and fauna, of the physical, chemical, and biological complex of an anopheline breeding-place. In fact Weyer[1] considers that salinity is not the decisive determining factor in the relative prevalence of *atroparvus* and the other races of north Germany, owing to the inconsistencies brought to light by accurate measurements in almost any locality. Lamborn[2] believes that the resultant of all the attractions exerted by a breeding-place is an appeal to the sense of smell. 'The female mosquito', he writes, 'like other insects is probably influenced in her choice of breeding places primarily by the odours characteristic of particular spots which connote the general suitability of the situation as to temperature, composition of water, and presence of particular foods.' Observations by Lewis in Albania point to the influence of certain aquatic plants as having an attractive and stimulating influence on ovipositing females, different groups of plants appealing to different races or species.

Unless, therefore, two different species happen to like the same conditions, we would not expect serious competition for water rights among our *maculipennis* larvae since the salt-water races inhabit different regions and the others are kept apart by their preferences for different types of water. How-

[1] *Arch. f. Hydrobiol.* **27** (4): 595, 1934.
[2] *Bull. Ent. Res.* **13** (1): 1, May, and (2): 129, Aug. 1922.

FIG. 11. FRESH-WATER BREEDING-PLACE OF *ATROPARVUS* IN WESTERN SPAIN

FIG. 12. A GENERAL BREEDING-PLACE
Macedonian pool breeding *maculipennis* (*typicus*, *messeae*), *elutus*, and *superpictus*

ever, until recently, our notions about anopheline egg-laying on different kinds of water have been derived mainly from catching the bred-out adults in near-by shelters. Barber[1] has now devised a simple method which enables us to find the eggs in natural breeding-places before they are hatched. Unlike the larvae and adults, the eggs can always be told apart. It turns out that there is a good deal of apparently careless egg-laying by all races and species. Martini[2] mentions finding all three of the northern types (*typicus*, *messeae*, and *atroparvus*) in the same pool of brackish water at Sülze in Mecklemburg (salinity 3·09 parts per thousand), while at Elmenhorst, in the valley of the Warnow, he found all three egg-types in fresh water. Barber has, as one interesting exhibit, a small spring-fed pool in northern Greece in which he has found the eggs of four different anopheline species (Fig. 12).

This is rather disconcerting and makes us wonder how much discrimination the ovipositing female actually shows. We might understand such a mixture of egg-types in borderline situations possessing overlapping characters and a wide range of appeal, or excuse a few misplaced eggs now and then as blunders in the dark. Probably the predominant race in a locality will always try to spread into waters not strictly its own. But the difficulty goes deeper than this. Swellengrebel writes: 'On more than one occasion we observed ditches in fresh-water areas situated close to brackish areas where nearly all the ova were *atroparvus* but the larvae collected were mostly *messeae*' (a fresh-water species). And it is not uncommon to find a decided prevalence of one race in the water and a virtual monopoly on the part of a different race of the near-by shelters. Of course, one race may be less disposed than another to enter shelters. Still, this definitely raises the question: do all the eggs eventually

[1] *Riv. Malariol.* **14**, sec. 1 (2): 146, Mar.–Apr. 1935.

[2] For a general discussion of the whole matter, see Martini, E., *Entom. Beih. aus Berlin-Dahlem*, **1**: 28, 7 Aug. 1934.

produce imagines or only those which are adapted to the breeding-places in which they find themselves? This is a revolutionary idea. Is it possible that anophelines are not guided after all by an instinct which enables them to judge in advance whether a given water-surface will offer conditions of food, temperature, and protection to their larvae, but merely scatter their eggs indiscriminately on every kind of water, trusting that a sufficient number will find favourable situations in which they can compete successfully with other forms? Nature is never parsimonious where reproduction is concerned, and experimental tests clearly lend support to the idea. As we have said, given the choice of fresh or slightly saline water in the laboratory, *messeae* and *atroparvus* seem to act in the most hare-brained way. More *messeae* than *atroparvus* may lay eggs in the salt solution, and *atroparvus* definitely prefer the fresh water. In fact, many insects will unhesitatingly deposit their eggs on injurious solutions in which hatching is out of the question.

As far as I know no laboratory or field experiments have as yet been devised to prove or disprove the existence of larval competition. There is evidence in nature both for it and against it. Selection on the part of the insect of salinities within certain definite limits can probably be ruled out. The coastal waters of Germany are much fresher than those of Holland, and the salinities in which *messeae* is habitually found in Holland are the same as those which characterize the breeding-places of *atroparvus* in Germany. Where several races occur together it is hard to imagine that any one breeding-place will possess such balanced characters that one race will not have at least a slight relative advantage over the others. It is not unusual to find that two or more races are jointly and successfully using the same breeding-place together with a rich fauna of other aquatic animals and insects. But this is not a simple mixture of races in a pool. It is a nicely adjusted community in tense and dynamic

balance. It is the usual condition in nature to have more individuals produced than can possibly survive. Slight changes in conditions, brought about by adverse seasons, by evaporation or rain, by causes of which we have no inkling, will alter the balance in favour of one or another form or may eliminate them all. And not only from season to season but from one year to another, there may be a profound change in the composition of the anopheline population. Thus, while the total anopheline output of a given water-surface may be fairly constant, the conditions favouring one race or another are never static and are always in the act of pushing one group out and inviting another in.

Our feeling that competition in a constantly over-stocked breeding-place must act to the disadvantage of imperfectly adapted forms is at present supported by logic rather than by observation or experimental proof. Pond,[1] in discussing the distribution of aquatic plants, says that 'competition of species for space may be considered a factor in distribution although it operates quite locally and does not work to modify the flora of large areas. *Chara* is infrequent on the alluvial bottoms where other species are present in abundance, but this is not because it prefers poorer soil, but because it is prevented from occupying the soil of its choice by the other species.' Swellengrebel has noted that *atroparvus* may take possession of ditches of low salinity in August, which were previously occupied by *messeae* throughout the summer but were abandoned when *messeae* went into early hibernation. Is this an example of one race keeping another out of certain breeding-places to which it would otherwise resort, or do the water conditions change as the season advances? Martini noticed in Sülze that the proportion of one race to another changed in the course of the year. In our Albanian studies Lewis has found that changes in the relative numbers of *maculipennis* races may

[1] In Ward and Whipple, *Fresh Water Biology*, ch. 7, p. 195 (New York and London, 1918).

be very striking. There are at least four races present in Albania, including a new fresh-water variety *subalpinus*, and they are all able to produce large populations because each prospers best under seasonal conditions not quite suitable to the others. Thus the same water, depending on its temperature, the amount of shade, its depth, its salt, and a complex of unknown factors, can serve each race in turn throughout the long summer: first *typicus* for a brief period, then *messeae* till apparently the water becomes too warm, then *subalpinus* until its limit of tolerance is reached, and finally *elutus*, which has its own private reserves of saline water but can also breed in fresh water under conditions which render this unsuitable for the rest. In all this there will be considerable overlapping, and perhaps none of the races will completely disappear from the marsh. That any one of them might breed throughout the summer in respectable numbers provided all the others were absent cannot be proved. We know that the larvae of all races and species of anopheles will grow for us and produce adults in dishes of tap water provided with the same food and intensity of light. Even *plumbeus* and *superpictus*, which are never by any chance found together in nature, will do very well under identical conditions side by side on a table in the laboratory. *A. maculipennis* will develop from egg to imago in pitch darkness, or, as Puntoni[1] has shown, in dilutions of sewage. Why are they not found in such situations in nature? It is probable that they find themselves at a disadvantage in such atypical waters in competition with more perfectly adapted forms and are consequently suppressed by them. Those with a wide range of adaptations cannot compete with those possessing very special adaptations, in the latter's strongholds. It might be objected that they do not even make the attempt, for they do not lay eggs on many types of water in which they can be bred out in the laboratory, and hence no actual competition with or suppression by other forms occurs. To that the advocate of competition would reply that this is the result of 'battles long ago' and that after aeons of trial and elimination they now avoid instinctively the places in which they have invariably failed to maintain themselves.

[1] *Riv. Malariol.* **13**, sec. 1 (6): 721, Nov.–Dec. 1934.

SEASONAL DISTRIBUTION OF VARIETIES OF A. MACULIPENNIS IN SIX ZONES OF ALBANIA, APRIL TO SEPTEMBER 1934 (BASED ON 3987 BATCHES OF EGGS)

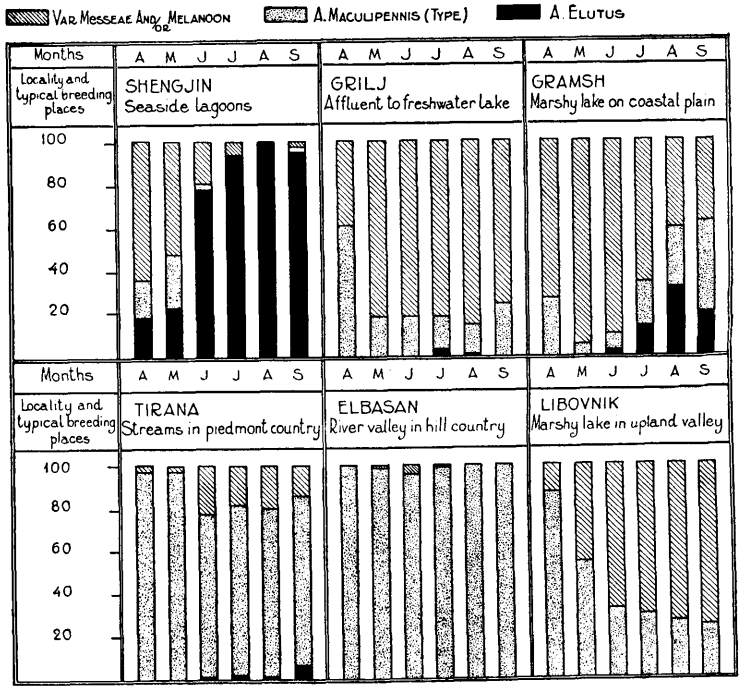


FIG. 13. In each area different races in different months find suitable conditions in the same water-surface.

But if competition is a natural factor in all biological communities, so is a delicate instinctive sensibility for favourable and unfavourable conditions. Wesenberg-Lund points out that ovipositing females of a certain culicine in Denmark can select the sites of future ponds six months ahead of the time when snow-fall will start to create them,

picking out such situations when there is no obvious depression in the terrain to indicate the sites to the human eye. Thus the mosquito exercises judgement, although it may be permitted a considerable latitude of choice. The same water is successfully used by several different forms. There are, however, limits of tolerance well known to the insects themselves. In Macedonia, Barber and Rice found that *elutus* can and will often associate with *maculipennis* in fresh water, but *maculipennis* cannot follow *elutus* into brackish lagoons. It does not even attempt to lay eggs on unsuitable water. Some fresh-water pools near the sea had both *elutus* and *maculipennis* eggs in August, but early in September a high tide made one of the pools brackish. No more *maculipennis* eggs were ever found in it, though they remained common in the other pools, and *elutus* continued to breed in them all. But even *elutus* refuses to lay in water that is too salt, or in sea water. 'Apparently', remark the observers, 'neither species has to lay eggs in water to find out whether it is suitable for breeding or not.'

The fact is, we have not yet gone about the study of larval ecology in a systematic way. The naturalists have recorded an immense number of random observations, but an analysis of these, instead of helping us, has practically destroyed all our handy generalizations, for investigators are always divided into those who are looking for rules and those who are looking for exceptions. The data, however, besides being uncoordinated, are essentially 'unweighted', so that it is hard to tell the fundamental and important from that which is merely local or unusual. For example, Swellengrebel records the fact that in Java, when the fish-ponds at certain seasons grew too salt for *ludlowi*, its larvae could be found in fresh waters, and he warned Walch that, if he succeeded in rendering the fish-ponds unsuitable for this species at all times, he might drive it *en masse* to occupy the near-by marshes, which were

extensive but harmless; and this point was strengthened by the fact that a form of *ludlowi*, indistinguishable by any structural character, was actually breeding in fresh water in Sumatra. Nevertheless, Walch proceeded to sanitate the fish-ponds, and the *ludlowi* proved to be unable to adapt themselves to the fresh water in Java in effective numbers. The few who did so were exceptional cases, and, while the naturalist was correct in recording the fact that *ludlowi* larvae were to be found in both fresh and salt water, the observation when properly 'weighted' proved to have no practical significance. But we are still in the dark with regard to the fundamental preferences of our European larvae, and an excellent illustration is the fate of the very generalization with which this discussion began. For years we have been dividing the *maculipennis* races into fresh-water and salt-water breeders; now we see this distinction relegated to a secondary position, with nothing to put in its place. It is about time to mobilize some chemists, physicists, and experimental biologists to control these energetic and iconoclastic field-workers with their dip-nets, microscopes, and thermometers. The malariologist wants more exact information about those nicely adjusted factors which permit the breeding of one kind of anopheline and not that of another. He would like to be able to intervene in such situations in a less costly way than with larvicides and drainage.

We have got hold of two very fundamental facts which throw light on the cause and distribution of malaria in Europe. Malaria, an entomological rather than a social problem, exists where certain anophelines with peculiar feeding habits can maintain themselves in sufficient numbers to ensure transmission. These dangerous anophelines are not distributed at haphazard, but occur in relation to certain combinations of chemical, physical, and biological characters of surface waters. What these characters are

which are thus correlated indirectly with malaria, and whether the mosquito carefully chooses them, or is excluded from places which do not have them by the competition of other forms, are questions still without an answer. The weight of evidence, in the words of Lamborn, is on the side of an 'urge to oviposition rather than an elimination of wrongly placed ova'. We know to our sorrow that the malaria carriers of the *maculipennis* group are the most adaptable and least specialized of the races. It is they who breed in both ponds and rivers, bite man and animals, use fresh water or salt, hibernate or not, according to circumstances. Studies of their physiology, their habits and instincts, and their place in nature have not led to a general clarification but rather to the uncovering of new problems, not previously suspected. Thus is the myth justified that malaria was the Hydra which Hercules conquered in Argos, and which grew two heads for every one cut off. Like Hercules, we must perforce leave some of the heads under a stone while we turn to other labours.

V

THE COMPLEXITY OF THE MALARIA PARASITE

Can any man, can all the Men in the World, though assisted by Anatomy, Chymistry and the best Glasses, pretend positively and certainly to tell us what particles, how sized, figured, situated, mixed, moved, and how many of them, are requisite to produce a quartan ague, and how they specifically differ from those of a tertian . . .?

THOMAS FULLER, *Exanthematologia* (1730)—quoted by THAYER.

LAVERAN, who discovered the parasite of malaria in 1880, thought there was only one kind of plasmodium in human beings, and that the three so-called species, so different under the microscope and in the clinic, were merely transient modifications of a single form, brought about by latitude, season, the resistance of the body, or some other environmental influence. The unicity theory of the malaria organism sprang from the observed fact that one type of parasite frequently changed into another during the course of the disease, under conditions which excluded the possibility of a second infection. The older malariologists were puzzled to find a patient, cured of *falciparum*, relapsing with *vivax*—a thing noted frequently in soldiers invalided home for malaria during the Great War. The idea grew up of a tricky adversary which, like the Old Man of the Sea, could alter its aspect and even shift its point of attack to meet defensive changes in the host. Almost every one is now agreed that such cases arise from mixed infections which have a curious way of taking alternate possession of the body. In fact, it was surprising to find that some one was interested enough in the moribund unicity theory to start an attack on it as recently as 1930, at the International Malaria Congress at Algiers. No one came forward to defend it, but some new evidence against it had appeared and I presume it seemed a pity not to use it.

The new evidence was provided by therapeutic malaria, which began to be used by Wagner-Jauregg[1] in 1917 in the treatment of general paralysis of the insane. It was a kindly turn of nature to make one disease a cure of another. The insuperable difficulties in the way of knowing all about the conditions surrounding any infection of malaria in nature made malariologists welcome this new field of observation and research afforded by an unusual kind of laboratory animal, man himself. Man has often volunteered in the interests of science to become a laboratory animal for the purposes of a crucial experiment and has willingly contracted more dangerous diseases than malaria, but for the first time human beings were now eager to be inoculated with one of the major diseases of mankind for their own benefit. All three types of malaria fever were tried out in turn, and under controlled conditions and continuous observation each recognized species of plasmodium remained always true to type, not only in mixed infections but even in the presence of a high degree of resistance on the part of the host. Knowles and Das Gupta[2] in 1932 thought for a moment that one of their monkey parasites had changed its character on inoculation into a new species of host, but this, too, turned out to be a concealed double infection.

Therapeutic malaria has done more than merely uphold the established triumvirate of malaria; it has given its support to a new candidate. In 1922 Stephens[3] had reported a new form which he called *P. ovale* in a patient who had contracted malaria in East Africa, and in 1927 the same form appeared again in a case from Nigeria. The parasites resembled a sort of cross between *P. malariae* and *P. vivax*. The infected red cells were only slightly enlarged as in quartan, but they were stippled with Schüffner's dots as in benign tertian. The scarce sexual forms were like those of

[1] *Psych.-Neurolog. Wch.* **20**: 132 and 251, 1918–19.
[2] *Ind. Med. Gaz.* **67** (6): 301, June 1932.
[3] *Ann. Trop. Med. & Paras.* **16** (4): 383, Dec. 1922.

malariae, but they always occurred in patients with tertian paroxysms. The name came from the oval form assumed by the parasitized red corpuscle, which was often drawn out into ragged points (fimbriated) at one end. For the rest, the parasite was small, showed little amoeboid movement, and when it divided produced only a few daughter cells or merozoites, eight or ten on the average. It turned out that Craig had noticed the same form, without giving it a name, in soldiers returning to America from the Philippines, and later Mühlens saw it in a South American patient. So the scattered observations drifted in from different parts of the world, but without any convincing continuity.

In 1930 Yorke and Owen[1] came across another good example of this form and were now able to keep it under observation by passing it through paralytic patients. Its characters remained constant through several passages by blood inoculation. In 1931 James[2] received from Yorke the blood from a Belgian Congo case and was able to infect mosquitoes with this new organism, although gametocytes were rare. He was later equally successful with a Nigerian strain, and retransmitted them both to man. The clinical course of the disease was exceptionally mild. The interesting thing, according to James, Nicol, and Shute,[3] is that at two stages of its life-cycle in *Anopheles maculipennis* its morphology is quite different from that of any of the three 'classical' species previously recognized: (*a*) in the arrangement of pigment granules in the seventy-two-hour oocyst in the stomach-wall of the mosquito, and (*b*) in the size of the sporozoites in its salivary glands, 'so much smaller than those of *P. vivax* that no one who examines preparations side by side could doubt that they belong to different species'.

Nevertheless, there are doubters still. Missiroli and

[1] *Ann. Trop. Med. & Paras.* **24** (4): 593, Dec. 1930.
[2] *Trans. Roy. Soc. Trop. Med. & Hyg.* **26** (1): 3, 30 June, 1932.
[3] *Ann. Trop. Med. & Paras.* **26** (2): 139, 14 July 1932.

Siniscalchi[1] found that even half a dozen direct passages of *P. vivax* from man to man, without the intervention of the sexual forms and their conjugation in the stomach of the mosquito, made the organism smaller, less mobile, and less prolific. Now there is one strain of *P. vivax* that has been propagated in this asexual fashion for over fifteen years, the one which Wagner-Jauregg isolated in the Balkans in 1919 and has used ever since in Vienna without once passing it through a mosquito. Giovannola[2] brought this strain to Rome and confronted it with other parasites of benign tertian. Whatever it may have been in the beginning, this plasmodium is now extraordinarily small, being hardly more than half the size of a Madagascar mosquito-born strain obtained from James's laboratory in England; and any one who 'examines the preparations side by side' would hardly doubt that they belong to different species, though both are *P. vivax*. In short, the Viennese parasite shows almost all the features described by Stephens as characteristic of *ovale*: namely, oval and pointed red cells, small globular schizonts with hardly any amoeboid movements, premature division with few daughter cells, and scarcity of gametocytes.

This is not the place to argue the status of *P. ovale*, or to speculate on its resemblance to a parasite which for many years has been multiplying asexually. What arrests the attention is the variability of *P. vivax*. Even the Madagascar strain, cultivated as it has been in mosquitoes, is definitely smaller than the Italian strain used in our laboratory. Was it smaller in Madagascar or has it been modified by its long habitat in refrigerated English anophelines? At any rate, its characters are now fixed, and like those of *ovale* and the plasmodium of Wagner-Jauregg remain constant in every vicissitude of transmission and storage. Not only have we, then, the regular *falciparum*, *vivax*, and quartan types of the

[1] *Riv. Malariol.* **8** (3): 251, May–June 1929.
[2] *Am. Jl. Trop. Med.* **15** (2): 175, Mar. 1935.

malaria parasite; we have several kinds of *vivax*, and, for all we know, of the others as well. There is, for instance, *P. tenue*, which is in much the same position as *ovale*, an aspirant for higher honours. Many have thought that its peculiar characteristics are due to some immune reaction on the part of its hosts, and others have considered it frankly an artifact. Perhaps some one is even now testing it in malaria therapy and will give us the final word regarding its position.

But malaria therapy has also revealed differences in the parasites which cannot be detected by the microscope. One of the first things noticed was the ease with which it was possible, with a very small dose of quinine, to put a stop to the most severe attack, whether caused by inoculation or mosquito bite. It was first thought to be due to the fact that general paralytic patients in England were all primary cases and hence more easily cured. This now seems to us to be a curious conclusion, for primary attacks are generally the hardest to control in nature; but it used to be thought that cases grew more chronic and intractable the longer they had the disease, till eventually they became quinine-fast, that is, some of them established a resistance to quinine and a life-long attachment to the disease.

The Madagascar strain, first used by James at Horton Mental Hospital, turned out to be a rather virulent one, and little as it required in the way of treatment to cut short the series of paroxysms, other strains, in other lands, required even less. Thus, in Mark Boyd's[1] series of *vivax* infections in Florida, almost all recovered spontaneously after a considerable number of paroxysms and needed no drugs at all. It is evident, then, that the body may finally overcome the infection in malaria by developing a resistance just as in any self-limited disease, and in fact our ancestors had no other recourse than their own natural forces when 'down with fever'.

[1] *South. Med. Jl.* **27** (2): 155, Feb. 1934.

Is there perhaps a true immunity in malaria? It is hard to reconcile this conception with that of an endlessly relapsing disease. Even after spontaneous recovery, in which nature has been allowed to take entire charge of the case, victory on the part of man is often a very short-lived one. Almost 60 per cent. of Boyd's cases relapsed, and even after the recurrence 60 per cent. relapsed again. Boyd was not able to infect his patients with the same parasite during the latent period, but tolerance of superinfection is not exactly the same thing as true immunity. There has been a good deal of discussion as to what we should call this condition of resistance to the malaria parasite. Sergent[1] proposed the term 'premunition' as characterizing the sort of tolerance arising in protozoal diseases, which causes them to resist superinfection as long as the parasite is present. But if the parasite has been completely eradicated and the resistance persists, we have a true immunity. In doubt as to whether we are dealing with a mere tolerance to the parasite while it is actually in the body, or with a premunition against superinfections with the same kind of parasite while the original infection persists, or with a true immunity which lingers even after the complete eradication of the original infection, we must fall back upon some such phrase as 'active defence mechanism' if we desire to be strictly accurate. In general we can fall into no very serious error by using the term 'immunity' to cover all such phenomena.

Sergent has said that premunition, in bird malaria at least, always disappears at the same time as the parasite, since cured birds, when reinoculated, have normal attacks. But this test does not tell us when the parasites disappeared. It may be that immunity lingered on for some time after the last parasite was gone; we can only infer that it does not last for ever, or that it is not continuously effective. The principal difficulty is that

[1] *Trans. Roy. Soc. Trop. Med. & Hyg.* **18** (4): 383, 25 Jan. 1925; and *Suppl. Riv. Malariol.* **14**, sec. 2 (3): 5, May–June 1935.

we have no independent proof that the bird is cured. We judge that it is cured because it can be reinfected, and then we conclude that it can be reinfected because it is cured. As a matter of fact it is virtually impossible to say when a cure has been achieved in malaria, and of this I shall give some startling illustrations farther on. No amount of negative evidence can be taken as conclusive. In practice we often tell a patient that if he shows no clinical symptoms for an entire year he will probably be free from further clinical manifestations, but we cannot guarantee the absence of parasites. After much experience Boyd does not venture further than to say that he thinks it probable that some degree of acquired immunity may persist after the complete disappearance of the malaria organism.

The experience of James[1] was with a much more virulent infection than that which, in Boyd's hands, so often produced merely the proper number of paroxysms for a course of treatment of general paralysis and then recovered spontaneously without giving further trouble. The parasite which James used came from Madagascar, and treatment was usually required to stop the attack. After the primary attack the tolerance was only relative, and the patient could generally be successfully infected a second time during the latent period. The first recurrence was, however, less severe and would often terminate spontaneously. After the primary attack and its first recurrence, especially if that had recovered without treatment, there was established what appeared to be a complete resistance to any further infection with the same parasite over a long period of time, amounting perhaps to several years.

James[2] has reported a very remarkable case which brings strong support to the immunity concept. His patient was infected with the Madagascar strain of *P. vivax* in January

[1] *L.o.N. Hlth. Org. C.H./Mal./57* (1), Geneva, Mar. 1926.

[2] Discussion of Thomson, *Trans. Roy. Soc. Trop. Med. & Hyg.* **26** (6): 483, May 1933.

1926, and had four recrudescences with spontaneous recovery. Eight months later parasites reappeared with fever, but she again recovered spontaneously, although fifteen days later there was a recrudescence. After a year without symptoms, mosquitoes infected with the same organism were again applied, three times in 1928 and three times in 1929. On each occasion a different batch of heavily infected mosquitoes was used—405 in all—without any reaction either parasitic or febrile. She was then inoculated with a mild strain of *P. falciparum*, which produced a severe attack. Two months later she was still immune to *P. vivax*. A year later she was infected with *P. ovale* and had a typical attack, after which she was shown to be still resistant to the original strain of *P. vivax*. James considers this to be a case of persistent immunity after the complete disappearance of *vivax* parasites.

James's striking case also showed that repeated inoculation with a rather virulent strain of benign tertian over a number of years gave not the slightest protection against the mildest of all known parasites, *P. ovale*. Immunity was shown to be exceedingly specific, and the unicity theory seemed to be finally sunk, though not without a trace. It was still to be raised once again, like an old warship, to be made the target for new guns.

Ciuca,[1] in Roumania, has tried to see how high this immunity can be pushed by direct blood inoculations. Blood inoculation of the malaria parasites differs from mosquito transmission in several ways. There is a much lower percentage of successful inoculations, the clinical course of the disease is shorter, and there are virtually no relapses. Ciuca started with 1,200 patients whom he inoculated with an indigenous strain of benign tertian, and continued to reinoculate with the same parasite as long as any were receptive to infection. Many were resistant to start with, since Roumania is a malarious country and a previous attack of

[1] *Trans. Roy. Soc. Trop. Med. & Hyg.* **27** (6): 619, May 1934.

malaria, even in infancy, seems to raise a higher threshold against infective blood inoculation than against infections transmitted by mosquitoes. About 34 per cent. did not come down with a primary attack, and 16 per cent. more became temporary carriers of parasites but without clinical symptoms. The second inoculation was successful in 13·5 per cent. of those infected the first time; the third succeeded in only 2 per cent., the fourth in 1·8 per cent. of these, while the fifth did not produce an attack in a single case. These non-susceptible individuals were immune to as much as 150 cubic centimetres of virulent blood, or to as many as twenty-five bites by infective anophelines. The percentage of spontaneous cures rose with the successive reinoculations, showing a progressive increase in immunity which evidently depends on the number of inoculations, as with bacteria. Some of the immune cases were proved to have latent infections, and therefore these had acquired premunition, as described by Sergent, but in the others there was no evidence at all of the persistence of the parasite. Even by transfusing great quantities of their blood into non-immunes, no latent infection could be proved. Ciuca considered the phenomenon one of true acquired immunity.

The direct inoculation of parasitized blood from one patient to the next is the method most commonly employed in malaria therapy, but it has become more and more evident that laboratories equipped to transmit malaria by anophelines infected with known strains are a more powerful instrument for the study of natural clinical malaria and its immunology. Infections following the inoculation of sporozoites by mosquitoes differ in almost every particular from those obtained with merozoites by blood transfer—in number of takes, in the effect of treatment, in the frequency of spontaneous cures, in gametocyte production, in relapse rate. Following the British example, such stations were soon established in Amsterdam and Rome, while that in Roumania, of which we have just been speaking,

has now turned as well to the insect transmission of the disease. Such stations have remained few as yet in Europe, because it is not a simple matter for the ordinary psychiatric clinician to establish a colony of anopheles in captivity and to use them for malaria transmission.

For some time these laboratories have been exchanging their parasites, which are usually sent by air mail, in infected mosquitoes. De Buck[1] had long thought his indigenous strain somewhat different from that used by James at Horton. It had a longer incubation and a different clinical course, since the cases always began with a true tertian type of fever instead of the quotidian form so characteristic of the Madagascar strain. When the latter was brought to Amsterdam and compared with the Dutch strain in patients lying side by side in the same room, the parasites proved to be even less alike than had been suspected, and the indigenous Dutch malaria to be almost a different disease from the benign tertian of Madagascar. The Dutch strain gave higher fever and was less susceptible to treatment with salvarsan. It was less virulent, and often produced no immediate primary attack but went into a long latency of several months, a phenomenon which occurred in 40 per cent. of the Dutch cases but only in 6 per cent. of those inoculated with the Madagascar strain. This was not a question of season but of some inherent quality, for it was true at any time of year. The parasites themselves were somewhat dissimilar, the indigenous strain having fewer daughter cells upon division, which accounted perhaps for its longer incubation period: twenty-one days as compared with an average of twelve days for the Madagascar malaria.

The most important fact perhaps was that there was no cross-immunity, so that a patient infected with the foreign strain would come down with a typical attack upon reinfection with the milder indigenous strain. Immunity seemed

[1] *Am. Jl. Hyg.* **24** (1): 1, July 1936.

not to be connected in any way with the virulence of the organism. Many similar differences were recognized in Rome and in Roumania upon the introduction of the Madagascar parasite. For instance, Ciuca reported that the Madagascar strain had produced as many as 400 flagellating forms (male parasites) in a cubic centimetre of blood, whereas in the indigenous strain he had never obtained more than 200 in a very large series of cases.

There is no question, therefore, of a simple modification of the benign tertian parasite. It is evident that *P. vivax* is not a unit but is merely a collective name for a wide variety of forms, immunologically distinct. We are only at the beginning of these studies; we do not know whether in limited regions there may not be genetic affinities between strains of the same parasite. For instance, Ciuca has found a considerable cross-immunity between the indigenous strains of benign tertian in Roumania. Only 13 per cent. of his cases after multiple inoculation with one strain were receptive to a new strain, and 90 per cent. of these recovered spontaneously. The possession of certain immune elements in common between *vivax* strains is to be expected, but it is less clear in human than in monkey malaria. It may be that sporozoites injected by mosquitoes break down barriers which are effective against inoculations with the merozoites of infected blood.

Are there also multiple strains of *P. falciparum* and *P. malariae*? We have not the same wealth of experience with these that we have acquired with *vivax*. There has always been a certain difficulty in their experimental transmission. In England the anophelines could not even be infected with the Indian or African malignant tertian strains.[1] Before so much was known about the differences between strains, it was suspected that this might be due to climate or some other environmental factor. There was an exchange

[1] James, S. P., Nicol, W. D., and Shute, P. G., *Proc. Roy. Soc. Med.* **25** (8): 1153, June 1932.

with Rome, and in both places the British anophelines were very receptive to infection by the Roman and Sardinian types of *falciparum*. When human infections with these strains were compared at Horton with those of the Indian and African parasites, it appeared that, as in the case of tertian, there were remarkable differences in pathogenicity, virulence, and the tendency to relapse.

In England it proved very difficult to cure the attacks of Italian *falciparum* malaria. There was practically no cross-immunity with the Indian and African strains, which responded easily to treatment. Cases infected with the Italian organisms recrudesced for weeks, regardless of the method of treatment. Eight times as much quinine was required to bring the Sardinian subtertian fever under control as sufficed for the Indian form. This calls to mind the successes reported by Acton and Sinton in the treatment of British soldiers in India, which aroused some surprise in Panama and Italy. In India *falciparum* infections responded to ordinary quinine treatment more readily than *vivax*. Soldiers who left the plains with a diagnosis of malignant tertian relapsed with benign tertian in the hill stations, and never showed malignant tertian again. The quinine taken *en route* was sufficient to suppress *falciparum* but not *vivax*. But in Rome and Panama the majority of primary attacks required at least three weeks of continued and skilful treatment to bring about a state of relative tolerance.

We are now beginning to understand the inconsistencies and the contrasted results obtained with quinine in the hands of workers in various parts of the world. For 300 years treatment with quinine has given uneven results in different regions, and criticism has been directed against the method quite as often as against the efficacy of the drug itself. There has been a constant search for new rhythms in treatment, since it was supposed that, if quinine could be administered at precisely the right moment in the life-cycle of the malaria parasite and the deadly stroke could be

repeated from time to time in a certain consonance with the parasitic rhythm, a sterilization of the host might possibly be attainable. The specific value of each new method of treatment was supposed to lie in its irregular but carefully planned intermittency, and indeed the new combination was usually a brilliant success in the beginning, only to fall within a short time into desuetude and oblivion.

In malaria it has always been recognized that individuals differ greatly in their response to therapy. It was not known until very recently that each strain of tertian or of estivo-autumnal malaria is a problem in therapeutics by itself. The so-called standard treatments proposed for universal administration are clearly of slight value. As we shall see, there is probably an effective and an ineffective way of giving quinine in malaria, but the proper treatment is based upon the clinical course of the individual case and not upon any supposed uniformity in the general behaviour of the parasite.

The study of the quartan parasite has been still more difficult, for only a short time ago no one had succeeded in transmitting it at all by means of the anopheline mosquito; now several have done so, but with difficulty. Boyd[1] has perhaps been the most successful, carrying the infection through two successive human-anopheles passages in four whites and two negroes, both races being highly susceptible. At ordinary temperatures it took thirty-five days, on the average, after infection of the mosquito for sporozoites to appear in its salivary glands. The presence of quartan fever in any amount is therefore an indication of the longevity of the local anopheline vector. The incubation period in man was equally long, or longer, amounting in one case to forty-two days. In the negroes the infection was of short duration, in the whites if untreated the paroxysms continued at regular seventy-two-hour intervals for four or five months. The disease was more severe than benign

[1] *Am. Jl. Trop. Med.* **13** (3): 265, May 1933.

tertian, and the patients suffered more between accesses of fever. Gametocytes appeared only several months after the onset and were always rare, especially the male forms, which Boyd and Stratman-Thomas state are not accurately represented by any of the illustrations of this cell given in the standard works of reference. They experienced a succession of failures in attempts to infect mosquitoes till they learnt to identify the infrequent micro-gametocytes and refrained from applying mosquitoes before their appearance. Yet their characteristics are strikingly similar to those exhibited by the male gametocyte of other species. In short, it is hardly practicable to maintain a strain of quartan indefinitely except by inoculation, and even here the incubation period is often greatly prolonged, averaging thirty days, and once reaching fifty-six days in Ciuca's experience. Only de Buck[1] reports comparatively short incubations of fifteen days, suggesting that *P. malariae*, too, occurs in various strains.

We are always led to wonder, when thinking of quartan, how it can persist under natural conditions, since the incubation period in the mosquito is almost twice as long as the average life-span of the insect. Ross once said that we should be able to say something of the length of life in nature of the common vector of any parasite since it was bound, on the average, to be longer than the developmental cycle of the parasite in its tissues. Either quartan is an exception, or we are mistaken in supposing that anophelines on the average live only two or three weeks. Probably it is carried only by peculiarly long-lived individual insects. Quartan appears, however, not to be easily transmitted even in nature. Wenyon, on the Macedonian front during the War, found quartan parasites frequently in native children, but never in British soldiers. Nor did these soldiers show quartan infections in after years in England, when *vivax* and *falciparum* had faded out of the picture. It seems that the

[1] *Ann. Trop. Med. & Paras.* **29** (2): 171, July 1935.

chances of acquiring quartan, even in two or three years in a highly endemic region, are small. Under the most favourable conditions for study the chain which unites case to case cannot usually be traced. In European villages under close observation this form of malaria often seems to drop out of existence for several seasons, only to reappear suddenly without recognized antecedent cases. Some suspect other reservoirs of infection than man, and Marchoux has suggested that quartan may not be transmitted by anophelines at all, but by some other vector.

On the other hand, quartan malaria is equally hard to get rid of. It may in part be a question of relative immunity. Ciuca has shown that it takes much longer to establish immunity to *P. malariae* than to the other species. After five successive inoculations almost 20 per cent. of the cases were still receptive to new infections, and many became carriers over long periods. After ten to seventeen inoculations, however, resistance was very high, not only to the same strain but also to the quartan parasite brought over from Horton. We are still vague, therefore, about its immunology. It is all a part of what Marchoux has called the 'mystery of quartan fever'. Knowles and Senior White[1] have advanced the idea that it is perhaps the most ancient of the malaria organisms, coming down to us out of an archaic world, and, being ill adapted to present-day conditions, is now tending to die out because of some change in the mosquito, or of some change in man.

Much has been learnt from induced infections in human beings, but the flood of light thrown upon the obscure field of malaria by the rapid extension of the therapeutic use of the disease has served also to bring into view a vast array of new and intricate problems, unsuspected variables and unknowns underlying the more obvious phenomena. Scientists are accustomed to advances in knowledge which only seem to increase their ignorance and perplexity. Spencer compared

[1] *Ind. Med. Res. Memoirs*, No. 18, Dec. 1930.

scientific investigation to the work of miners digging in a cave. The more they excavated and the larger the space illumined by their dim lamps, the greater became their contact with the unknown and the unexplored. The paradox that our discoveries seem at times to push the goal still farther out of reach recalls the mystic utterance of Swedenborg that in revelation there is an obscuring and veiling over of the divine truth—a thought which the scientist can appreciate perhaps even better than the theologian.

For these newer problems of malariology, man has not proved to be the ideal laboratory animal after all. Experimentation on human beings is limited in several directions, since it must be restricted to that which will benefit the patient. It is concerned mainly with *vivax*, since virulent *falciparum* strains cannot be used without treating the patients continuously, and *malariae* is transmissible in practice only by blood inoculation. Patients cannot be sacrificed at interesting stages of their infection to have a look at their organs, deaths are few, and in these malaria is only a complication of the original disease which is being treated, and almost the whole field of experimental pathology is forbidden ground.

Birds, until recently, have been the mainstay of laboratory experiments. Two of the fundamental discoveries in malariology were made in birds: that of insect transmission by Ross, and that of the sexual nature of gametocytes by MacCallum. The organic chemist in his search for new drugs cannot possibly dispense with birds, since Roehl[1] with his oesophageal tube and quantitative methods paved the way for the recent advances in therapy with synthetic drugs. Canaries, which are not infected in nature, are very receptive to the plasmodia of the *Proteosoma* group which produce large numbers of asexual organisms (trophozoites) in the circulating blood. On the other hand, the rice-finches of the Far East are naturally infected with *haemoproteus*

[1] Quoted by Kikuth, W., *Suppl. Riv. Malariol.* **14**, sec. 1, (6): 71, 1935.

organisms which carry on their asexual cycle in the fixed tissue-cells, but throw out a rich supply of gametocytes into the blood-stream. The former can thus be used to test the effect of drugs on the asexual or schizogonic cycle, while the latter is indispensable for the testing of gametocides, so important in the preventive field of malaria therapeutics.

The efficacy of a given drug is not the same, of course, in bird infections as in human infections. It is not the same even for the same parasite in different species of birds. Thus the synthetic preparation known as Fourneau 710 is much more effective than plasmoquine on *P. relictum* in the small bird *Spinus spinus*, but less so in canaries, as it is also in human infections. The birds are, however, essential for preliminary tests and permit the discarding of thousands of preparations which fail to demonstrate any significant effect at all.

One of the most important fields of research in bird malaria has been in the mechanism of immunity. The foundation of our knowledge of this subject is due largely to the Taliaferros' studies of bird malaria. However, it cannot be denied that this differs in a great many important respects from the malaria fever of human beings. The observations and results cannot be directly used in the interpretation of human phenomena, but must pass through some sort of critical and experimental adaptation before their meaning becomes clear.

This is, of course, far less true of monkeys, which have recently been brought into great prominence in experimental malariology. It is rather surprising that their turn has come so late in the history of malaria research. Probably much time was wasted in trying to transmit to them the various species of human parasites. In 1917 Mesnil and Roubaud[1] succeeded in transmitting *P. vivax* to a chimpanzee, but this experiment has never been successfully repeated. Taliaferro[2] produced a transient infection of *P.*

[1] *C.R. Acad. Sci.* **165** (1): 39, 2 July 1917.
[2] *Am. Jl. Hyg.* **19** (2): 318, Mar. 1934.

falciparum in very small howler monkeys of Panama by using enormous doses of infected blood. There was a very sluggish response of the defensive lymphoid tissue in the monkeys, showing that the parasites were very easily disposed of. There were no gametocytes. People are still trying to infect some monkey with a human parasite, and it is not improbable that some one may eventually succeed with a particularly adaptable strain. The reciprocal infection, that of man with a monkey plasmodium, has, on the other hand, not proved difficult. Ciuca and his colleagues in Roumania infected man first with *P. inui* from a baboon and later with *P. knowlesi* from the Malayan monkey *Silenus irus*. This parasite has now been passed many times from man to man by blood transfusion, and is being used to induce therapeutic malaria in human paralytics. It causes a high fever, which responds promptly to quinine or atebrin, and there is little danger of its spread in the community.

It has lately been discovered that the natural malaria infections in monkeys behave very much like those of human beings. To establish certain fundamental concepts monkey malaria is more useful than bird malaria and more practical than malaria induced in human volunteers. The Indian monkey *Silenus* (*Macacus*) *rhesus* has been found suitable by Sinton and Mulligan[1] for experimental malaria because it is not infected in nature. There is on the contrary a high rate of natural infection in *Silenus irus* from Malaya and Java, and this has served as the source of infection.

S. irus is the natural host of at least two plasmodia which can be isolated and transmitted without difficulty. They have been recently described by Knowles and Das Gupta.[2] One is *P. inui*, which causes a mild infection in both *irus* and *rhesus* monkeys; they all recover spontaneously. It has a

[1] *Rec. Mal. Surv. Ind.* **3** (3): 381, June 1933.
[2] *Ind. Med. Gaz.* **69** (10): 541, Oct. 1934.

forty-eight-hour cycle like *P. vivax* of human benign tertian fever, and can be transmitted by mosquitoes. It forms a fine golden-brown pigment. The other is *P. knowlesi*, with a twenty-four-hour schizogony cycle like *P. falciparum*, and coarse greenish-brown to black pigment, but its gametocytes are round like those of quartan. The infection takes a mild course in *irus* monkeys but is invariably fatal in *rhesus* if untreated, and may cause haemoglobinuria just before death. It has been transmitted by mosquitoes in England. The African parasite, *P. kochi*, does not seem to be transmissible to other lower monkeys, but the American *P. brasilianum*, with its quartan cycle, has been very useful to Taliaferro and others.

The behaviour of these parasites in the body, the reaction of the tissues of the host, the clinical course, and pathology, all closely resemble the human disease, and we are on the threshold of explorations never possible before. It seems probable that the study of clinical malaria, its pathology and its immunology, have lagged behind that of other less important diseases, precisely because the study of malaria in nature is so extremely difficult. The investigation of malaria in the laboratory monkey, though laborious and time-consuming beyond that of the bacterial diseases, is extraordinarily rich in results, both for the confirmation of old theories and the follow-up of novel and hitherto unsuspected leads.

Sinton has already shown that there is no cross-immunity between the two Far Eastern parasites described above, even when both are isolated from the same monkey. He has furthermore obtained six strains of *P. knowlesi* (K 1–6) in addition to the original strain (C) already described by Napier and Campbell in 1932. A chronic or latent infection with one strain of either *P. knowlesi* or *P. inui* appears to confer an immunity against the clinical effects of superinfection with the same strain of parasite. But in testing out the cross-immunities between the strains, Mulligan and

Sinton[1] came across a rather curious and intricate situation. They attempted to infect the same monkey with all the strains of *P. knowlesi* one after the other, allowing the monkey time to recover from each infection before starting on the next. This naturally took a good deal of time (almost two years), and a complete series of infections has, in fact, not yet been reported. However, a tolerance to four different strains did not immunize monkeys to inoculation with a fifth. The primary infection was one of strain C, and a superinfection with strain K 1 caused an acute clinical relapse, which recovered spontaneously. A second superinfection with strain K 2 caused a distinct parasitic relapse with some anaemia, while a later superinfection with strain K 3 produced a very slight effect. Subsequently strain K 4 caused another parasitic relapse. It might have been expected that a very high degree of tolerance would have been produced in an animal which had been infected and superinfected with five strains of *P. knowlesi*, and in which a chronic infection had lasted for seventeen months. A fifth superinfection was made with strain K 6 on the 523rd day, and this proved rapidly fatal in spite of treatment. The interval between the last two superinfections in this case was about forty days. It is impossible to be certain that the severe effects of strain K 6 were not attributable, partly at least, to a concurrent relapse of strain K 4 superimposed on an acute infection. Strain K 4 has been found to be more virulent than any of the other strains investigated so far, and it has also shown a greater tendency to relapse.

In this lack of cross-immunity monkey malaria seems to differ from bird malaria, for Gingrich[2] has studied the effect of inoculating birds with five different strains of *P. relictum*. A latent or chronic infection with any one of the five is associated with an effective immunity to superinfection by

[1] *Rec. Mal. Surv. Ind.* **3** (3): 529, June; and (4): 809, Dec. 1933.
[2] *Jl. Prev. Med.* **6** (3): 196, May 1932.

any other strains. It would seem, then, that monkey malaria in this respect is much nearer than bird malaria to the human disease.

Sinton, however, was not able to give all of his strains to the same monkey. C and K 1 were plainly heterologous; i.e. there was no cross-immunity between them, and a monkey recovering from either would again have a normal attack if inoculated with the other. C and K 2 were also heterologous, as were K 1 and K 2. Any two of the three strains, then, would give successive and unmodified attacks of malaria to the same monkey. But whichever strains were used, the monkey would thereafter be resistant to the third strain, with which it had not been inoculated. Thus successive infections with C and with K 1 gave a tolerance to K 2, and similarly C+K 2 gave a tolerance to K 1.

The only explanation would seem to be that each of these strains contains immunological elements in common with each of the others. The simplest case would be as follows: C might contain, among others, certain elements X and Y, K 1 might contain X and Z, and K 2, Y and Z. Any combination of two would therefore contain elements $X+Y+Z$, and would be resistant to inoculation with the third strain. The real situation must, of course, be much more complex than this, and it would take a great deal of time and a large number of monkeys to work out the various permutations and combinations existing in the distribution of the various immunological elements, whatever they may be. Thus there are also interesting incomplete tolerances sometimes established. C+K 2 give only partial protection against K 4; i.e. there is a parasitic relapse but without symptoms. There are, therefore, elements in K 4 not found in either C or K 2. It is at least extremely likely that none of the seven strains of *P. knowlesi* is pure, but is itself a mixture. Sinton has suggested that possibly numerous inoculations might develop a slight degree of non-specific resistance to all strains of the same species, owing to a general stimulation

of the defensive reticulo-endothelial system by a certain number of infections. The great specificity which occurs in all experiments, both in human beings and in monkeys, makes this unlikely. Thus Boyd and Stratman-Thomas[1] found that, even when appreciable numbers of *P. vivax* are present in the peripheral circulation, the patient does not possess a tolerance to other strains of this parasite.

Partial immunities, partial tolerances might be explained by the loss of certain elements during the passages of composite strains, both in the laboratory and in nature. These elements might not be present in the circulation at the time the blood was taken or when the mosquito was biting, or they might be suppressed by the natural defences of the body. This would result in a gradual loss of immunity to those elements and an increasing susceptibility to reinfection. It recalls the situation in Roumania with regard to *P. vivax*, to which I have already referred. Ciuca found that after many inoculations only about one in seven of his patients were receptive to other indigenous strains of *vivax*.

It is only natural that the imagination of workers in this field has seized upon the existence of such strains to explain all kinds of obscure phenomena in malaria. Some infections produce more gametocytes than others, and Huff[2] reported a *cathemerium* strain in his birds which suddenly lost the power to produce sexual forms at all, and did not ever regain it in subsequent passages. If this faculty is under the special protection of a gene and can be lost by mutation, such strains would, of course, be snuffed out at once in nature, and those with few gametocytes would gradually be eliminated in competition with more strongly sexed neighbours. The tendency also of *P. falciparum* to select certain organs—the intestinal wall, the omentum, the brain—for localization has been explained by tropisms developed by certain strains.

[1] *Am. Jl. Hyg.* **18** (2): 482, Sept. 1933.
[2] *Am. Jl. Hyg.* **19** (2): 404, Mar. 1934.

Blackwater fever, the *bête noire* of the malariologists, has been attacked from this angle too. Giglioli[1] thinks its uneven distribution in the world points to the agency of specific parasites. From the Philippine Islands only two cases, according to Hasselmann,[2] have ever been reported with any certainty, while I remember, in the southern United States where I began my malaria studies, finding twenty-two cases in a single county in Georgia in one season; nevertheless the endemic malaria was so mild that, shortly after, the laboratory had to be moved to another region for lack of material. In the old world, on the contrary, blackwater is frequent in the tropics, unusual in the temperate zone. Yet it is a phenomenon not restricted to human beings. Knowles and Das Gupta have now reported haemoglobinuria in two of their untreated monkeys, infected with *P. knowlesi*. We are left still in doubt as to whether it is due to a specific strain or a disposition of the patient, or whether it is a form of malaria at all.

We are now at a point where we must admit a very great complexity indeed in the composition of the various recognized species of plasmodia. Not only are there possibly more species than we now describe, but each of these species is nothing but a collection of an unknown number of races or strains differing in almost every biological character, and each of these strains in turn may not be pure but may comprise a different assortment of immunological and other elements, part of which it owns in common with other strains of the same region. This is indeed very far from Laveran's hypothesis of a single malarial parasitic type.

[1] *Trans. Roy. Soc. Trop. Med. & Hyg.* **26** (3): 204, 30 Nov. 1932.
[2] *Jl. Philipp. Is. Med. Assoc.* **14** (1): 18, Jan. 1934.

VI

THE ROLE OF IMMUNITY

I had the honour of reporting to this Society . . . [5 June 1886], that it did not seem unreasonable to suppose that this fact [of phagocytosis] must be taken into account to explain the spontaneous termination of malaria infections. . . . Subsequently Metchnikoff, on the basis of my observations and three of his own . . . became convinced that in malaria fevers it is above all the macrophages of the spleen and liver that take upon themselves this function.

CAMILLO GOLGI, 1888.

ANY one who has just been exposed to malaria lives for a fortnight in a state of unpleasant suspense waiting to find out whether he has been infected or not. With all our improvements in diagnostic technique there is still no way of anticipating this knowledge. We say that the disease is incubating, but what is actually going on in the body is sealed in complete mystery, unrevealed by sign or symptom. The text-books teach us very simply and plausibly that the incubation period is the time required by the parasites to build up their numbers to the so-called *fever threshold* (the 'pyrogenic limit' of Ross) when the quantity of parasites in the body becomes so disturbing as to bring on an 'attack', characterized by a brief irregular prelude of rising temperature followed by a shaking chill and high fever.

Naturally, attempts have been made to assign a numerical value to this fever threshold. Years ago Ross and Thomson[1] (1910), studying some cases of malaria in seamen at Liverpool, made rough estimates of the number of plasmodia in the peripheral blood at the beginning of an attack, and these have been widely quoted and accepted ever since as representing the number which must be present in the circulation to produce fever. The threshold was not very well defined: in the case of *vivax* it varied from 200 to 500 organisms per cubic millimetre, and *falciparum* seemed to require three

[1] *Ann. Trop. Med. & Paras.* **4** (3): 267, Dec. 1910.

times as many, or 600 to 1,500. When we consider that an ordinary adult has something like 5 million cubic millimetres of blood, the grand total of parasites at the lowest count would run into thousands of millions before there would be enough in circulation to produce any symptoms. That this is not impossible can easily be demonstrated by a simple mathematical calculation in geometrical progression, the one so often used in poultry catalogues to show how prodigiously living things multiply if given a free rein. *Plasmodium vivax*, for example, divides every two days into about fifteen daughter cells, or merozoites, so that after seven generations (an average incubation for benign tertian) there should be theoretically almost 200 million parasites for every one injected by the mosquito, or a matter of milliards from a single infective bite.

Now while most of the books repeat these original calculations of Ross with some gusto, since we all relish the pleasant excitement of such large numbers, a little investigation shows that nothing like this actually happens. It is not that parasites cannot reach these densities. Babies in areas of highly endemic malaria may have as many as 10,000 to 100,000 plasmodia per cubic millimetre of blood, as Christophers[1] has shown. The trouble is, no such numbers can be demonstrated at the end of the primary incubation period. In fact, it is difficult to find any parasites at all. Yorke and Macfie[2] noted in their laboratory cases that the appearance of parasites in the blood very frequently coincided with the initial rise of temperature; sometimes the fever appeared a few days before the parasites, and very rarely the appearance of the parasites preceded the first rise of temperature. That this was not due to any hasty or superficial examination of the blood is shown by Boyd's[3] series. In 107 primary cases, parasites were not detected in thin smears, even by a

[1] *Ind. Jl. Med. Res.* **12** (2): 273, Oct. 1924.
[2] *Trans. Roy. Soc. Trop. Med. & Hyg.* **18** (2): 13, 15 May 1924.
[3] *Am. Jl. Hyg.* **20** (2): 488, Sept. 1934.

thirty-minute examination, earlier than the tenth day after inoculation, though in four cases a significant rise in temperature occurred earlier. In about two-thirds of these cases parasites were not discovered before the onset of the attack, and this quite independently of the duration of incubation, which varied enormously. The number needed to ensure a positive bloodsmear is therefore roughly the same as that required to produce symptoms. Our patient, who has been living in suspense all this time, will gain nothing then by sending daily samples of his blood to the laboratory in the hope of forestalling a possible attack.

Ross knew how hard it was to find parasites, but he concluded that it was not for lack of plasmodia, but because our methods of examination were unable to reveal them. He found that in fifteen minutes an experienced observer could examine with care only about one-fiftieth of a cubic millimetre of blood in an ordinary thin film. Thus, even if he were skilful enough not to miss any parasites, he could not hope to discover an infection until the organisms reached an average density of fifty to the cubic millimetre. Our patient therefore would already be host to at least 250 million parasites by the time a diagnosis could be made, and for ordinary routine examinations it would be conservative to multiply this figure by three or four. So something on this order has come down to us as representing in an approximate way the hypothetical fever threshold itself. For Ross's rule was this: 'We may I think accept the principle (pending more exact researches) that if we cannot find the parasites after careful search, their number is not usually sufficient to produce fever.'

Now the detection of parasites in the blood is mainly a question of technique, and any improvement which would enable us to examine larger quantities of blood in the same space of time would certainly lower the threshold of discovery. Ross himself invented such an improvement—the thick blood preparation—but it did not lead him to revise

his estimate of the pyrogenic limit, for a reason which we shall discuss farther on. But the thick smear was certainly a great advance. In it the red blood corpuscles are laked with water and the haemoglobin washed out. The cells become perfectly transparent, so that we can look down through layer after layer and pick up parasites at any level with our microscope. A good thick smear, one centimetre square, contains about 30 cubic millimetres of blood, and at least one-tenth of it can be minutely examined in fifteen minutes. Van Assendelft[1] in Schüffner's laboratory has reported by painstaking use of this method several parasite counts as low as one per cubic millimetre of blood, and in one instance he discovered an infection when the plasmodia were as rare as one in 3 cubic millimetres. In this case there could hardly have been more than 2 million parasites in circulation, and yet an acute rise in temperature had already taken place. This is certainly astonishing in view of what we have been told about the fever threshold and its relative constancy at a rather high level. Van Assendelft's patient must have been a peculiarly susceptible individual, for there can be no connexion, of course, between the number of parasites necessary to produce symptoms and the number needed for diagnosis. It was pure accident that with Ross's technique they turned out to be nearly the same. We should expect that with improved methods our diagnosis nowadays would anticipate the attack by several parasitic generations. This has not happened. We have succeeded in lowering the diagnostic threshold from 250 million parasites to 5 million or less, and still we cannot find the parasites until near the end of the incubation period.

Interested by these considerations, Boyd and Stratman-Thomas[2] caused a patient to be bitten by fifteen heavily infected mosquitoes, and every day thereafter for ten days injected 10 cubic centimetres of his blood into non-

[1] 'Impfmalaria', *Beih. Arch. f. Schiffs- u. Trop.-Hyg.* **35** (1): 1, 1931.
[2] *Am. Jl. Hyg.* **20** (2): 488, Sept. 1934.

immunes. In spite of such a heavy inoculation the infection was not transferred until the eighth day. It is clear that the plasmodia do not come up to our mathematical expectations. The numbers actually observed toward the end of incubation bear little or no relation to the estimated number of descendants of the sixth and subsequent generations. What has become of all these plasmodia?

It is possible that in natural infections there may be a very heavy initial mortality among sporozoites, so that only a few, and sometimes none at all, succeed in establishing merozoites in red blood cells. Much depends evidently on the dose of infection and perhaps on that mysterious quality (if it exists) which James calls vitality, and which is not the same thing as virulence. Both the number and vitality of living sporozoites are affected by the length of time they have been retained in the glands of the mosquito. Thus the infective material during epidemics is fresh and powerful, while in mild endemic or in sporadic malaria it is not nearly so effective. Ten days after a mosquito becomes infective, it is no longer certain to transmit malaria with every bite, and after 40 or 50 days it ceases to be infective at all. Sporozoites, too, may have to go through an adaptive phase in passing from a cold- to a warm-blooded animal, which would take time and postpone the stage of active multiplication. All these things would tend to modify the number of plasmodia and upset our calculations.

But Taliaferro[1] hit upon a more potent factor in his infected canaries. It is the factor which prevents all living things in nature from increasing at the rate set by the number of offspring. The great majority of the parasites are destroyed. They are eliminated by the ordinary defensive powers of the body. *P. cathemerium* of birds should increase fifteen times at each division, but ten of the fifteen daughter cells die from the very beginning, not because the bird has acquired any special resistance to the parasites,

[1] *The Immunology of Parasitic Infections* (New York, 1929).

but through the natural ability of the organism to protect itself from invaders. In monkeys[1] the proportion is even higher, seven out of nine merozoites being killed before maturity, and something of the sort must take place in untreated primary human infections. If each sporulating *vivax* leaves only three or four survivors, by the twelfth or fourteenth day its offspring will number but a few thousands instead of hundreds of millions.

Not that the mortality in each case and in each generation is necessarily the same. There are people who are more susceptible than the average. They may not kill twelve of the fifteen merozoites at each segmentation of the plasmodium. They may kill hardly any at all. On the other hand, in other individuals the rate of increase of the plasmodium might be cut down to such a degree as to suppress the acute attack altogether, leaving the parasite barely able to maintain itself in the bone marrow or some other retreat until the time came to take reprisals. The infection might be stamped out without coming to attack at all. The rate of increase of the parasites may thus conceivably vary from zero to a maximum represented by its natural reproductive powers. The degree of infestation of babies is particularly interesting in this connexion, for babies begin with only their natural powers of resistance to combat the plasmodium. Wilson[2] has studied infections in Bantu babies in Tanganyika Territory. All were infected by the fifth month, and by all three parasites in the second year. 'One of the striking features of this period of acute infestation, lasting about eighteen months, is the difference in the degree of infestation in different individuals. These babies were constantly being reinfected by fresh invasions of sporozoites. The difference cannot therefore be due to variations in the parasites, but rather to a variation in individual resistance.'

[1] Taliaferro, W. H., *Am. Jl. Hyg.* **16** (2): 429, Sept. 1932.
[2] *Trans. Roy. Soc. Trop. Med. & Hyg.* **29** (6): 583, 8 Apr. 1936.

More obscure than the human differences are the differences between strains of plasmodia. For years de Buck has maintained in Amsterdam two strains of *vivax*—'H', a Dutch strain with a twenty-one-day period of incubation, and 'M', an imported (Madagascar) strain with an average incubation of twelve days, a notable difference of nine days. Careful counting showed that 'M' produced eighteen merozoites at each division and 'H' only thirteen, and this was accepted for a long time as the explanation of the long and the short incubation. But de Buck has now pointed out that this cannot possibly be the reason, for at the time 'M' provokes symptoms 'H' is only one generation behind in numbers, but four or five in time. The solution is wrapped up in mysterious differences between strains. We must not fail to add that Ross himself took all these factors into account. 'The question', he wrote (of the quantitative estimation of the fever threshold), 'is probably determined partly by the skill and patience of the observer, partly by the susceptibility of the patient, partly by the "virulence" of the parasite.'

But if the rate of increase of the parasite in the human blood is subject to so many modifying influences, is this not compensated by the varying duration of the incubation period? In fact nothing in malaria is more uncertain than the interval between infection and attack. In a single consecutive series of 67 cases in our laboratory this varied from 9 to 23 days. If it could be shown that the longer periods corresponded with the smaller infective doses or a greater natural resistance on the part of the patient, the fever threshold would still have some standing. The size of the dose undoubtedly has an important influence on the course of the disease, but only a limited effect on the incubation period. It can be shortened, but not in proportion to the dose. James, who applied to single cases as many as 60 and 80 anophelines, later proved by dissection to be heavily infected, could not affirm that the 'incubation period is influenced significantly by the amount of the infective dose'.

De Sanctis Monaldi[1] dissected out the salivary glands of mosquitoes and counted the sporozoites before injecting them into patients. In one case 2,500 sporozoites caused an attack after 15 days, and 100,000, or forty times as many, after 17 days. On the other hand, quinine administered during the incubation period must surely reduce the number of parasites, but it does not delay the appearance of symptoms. James reports cases of patients who began their attacks while taking 60 centigrammes of quinine daily.

What is it then that determines the initial rise of fever in each individual case? Has the number of parasites nothing to do with it at all? We are unable to answer these questions at the present moment, simple as they seemed at the beginning of our discussion. Number and quality of sporozoites in the infective bite, and rate of increase in the blood are factors of such obvious importance in malaria infection that no one would dare to question their influence on incubation and onset of clinical symptoms without much more evidence than we now have at hand. Yet in a series of cases coming down with fever after the same number of days of incubation van Assendelft discovered an enormous disparity in the densities of the parasites at the moment of onset. Some individuals had as few as one plasmodium per cubic millimetre, and others more than 900. Perhaps there is no fever threshold at all even for each individual case. It is conceivable that host reaction rather than parasite density may initiate the attack.

Each plasmodium destroys a red cell, and therefore it must be the chief concern of the body from the moment of infection to keep down the number of parasites. It is evident from what we have said, however, that the normal qualities of the blood and tissues are not able by themselves, except in the rarest of cases, to stem the rising tide of infection and abort the attack. There are persons, it is true (and Celli mentions a number of cases), who have lived from

[1] *Riv. Malariol.* **14**, sec. 1 (4): 344, July–Aug. 1935.

birth in highly malarious places and have never, according to credible witnesses, suffered from malaria or taken treatment. Some are perhaps avoided by mosquitoes, but some may be refractory to the malarial organism. Normally, however, even the heaviest restriction imposed by the body during incubation on the natural multiplication rate of the plasmodium would not be able to prevent the parasites from eventually attaining any imaginable density, for the common character of all geometric progressions is that, however slowly they get under way, the curve soon bends sharply upward and the numbers soar with great speed to fantastic heights. Such is the picture we often get in fatal cases just before death in which parasites occupy every third red cell and are present literally by the million in each cubic millimetre of blood.

This does not ordinarily take place even in untreated primary cases of malaria. Something intervenes in time to prevent such a stampede—a new factor which rapidly puts the body on even terms with the enemy. During the incubation period, as Taliaferro showed in birds and monkeys, the parasites go on increasing at a constant though restricted rate despite a huge mortality, while the host, unable for the time being to strengthen his resistance, is condemned to fight a losing battle. The body, however, behind this crumbling defence gains just the time needed to organize its forces in a more specific way, building up a killing mechanism adapted to the particular enemy with which it has to deal. It seems that this mechanism cannot be brought very rapidly into play but requires a certain period for perfection, and in this it has much in common with the development of immune reactions in certain bacterial infections. At a certain moment, however, it sweeps into action, and if not too late it turns the tables on the foe. In the bird everything is risked on one battle—a crisis in which the parasites are almost totally destroyed, or the bird itself succumbs; in man there is a prolonged attack with many paroxysms. In either case a profound change has taken place rather suddenly. To the

natural qualities of the blood and tissues has been added a new power to deal specifically and destructively with a given race of malarial micro-organisms.

This is reflected in the clinical picture. The parasites which swarm in the blood are not so much attacking the body, as trying to live and multiply and eventually to emigrate before the situation gets uncomfortably dangerous. They are, in fact, always on the defensive. It is the body which is now attacking the parasite, with great destruction of cells on both sides. After an irregular start the fever takes its characteristic course, and the spleen begins to swell until it can easily be felt in children bulging below the ribs on the left side, a soft, elastic, spongy mass distended with blood. Abrami and Senevet[1] thought the malarial *rigor* due not to toxins but to anaphylactic shock caused by liberated merozoites or products of destroyed red blood corpuscles acting like foreign proteins injected in the blood-stream. The same idea has, of course, been used to explain the incubation periods of most of the common infections. The periodic manifestations of acute malaria are rather difficult to bring into the frame of anaphylaxis—those endlessly repeated *rigors*, for example, of untreated quartan fever which may go on at regular intervals for six months or more. The conception, however, has something in common with that which we have reached in our discussion. The initial latency in malaria seems to be the time needed by the body to prepare for war rather than that required by the plasmodium to reach a given density.

The true nature of the defensive preparations of the host was clearly perceived by Golgi[2] fifty years ago. On 19 May 1888 he presented a communication to the Medical Society of Pavia which has almost the sound of modern revelation:

'It is only too evident', he wrote, 'that if all the malaria parasites

[1] *Bull. Mém. Soc. Méd. Hôp. Paris*, **35** (19): 530 and 537, 12 June 1919.

[2] *Studi di Golgi sulla malaria*, Rept. by Inst. of Malariology, 1929 (ed. Pozzi, Roma), p. 35.

arriving at maturation should invariably complete their cycle so that the eight to twelve young plasmodia resulting from each segmentation should invade as many red blood-cells to recommence the process, it would be the rule for every malaria infection to progress inevitably to the pernicious stage. What happens instead is that with each paroxysm, and perhaps in part because of the febrile temperature itself, the white corpuscles account for the destruction of a conspicuous number of parasites, with such effect that in the cases which come under our observation it is the usual thing for the infection gradually to be extinguished. It is obvious that what we can see going on in the circulating blood is only a small detail of the whole process taking place so much more intensively in the spleen, bone marrow and perhaps the liver.'

Now leukocytes on ordinary scavenging duty in the blood do, without any previous experience with malaria parasites, pick up and destroy a great many of them along with other foreign particles—so many as to make a significant impression on their numbers. Taliaferro has now made clear the two stages of the defence: the non-specific destruction of plasmodia during the incubation period, and the specific reaction of the host during the febrile attack.

The Mechanism of Defence

The free leukocytes in the blood are the policemen of the body, but the regular army is made up of the great phagocytes known as macrophages, which live on the walls of the blood-vessels of the internal organs. These are normally present everywhere—in the liver, spleen, lymph nodes, and bone marrow, in the septa of the lungs and the meninges of the central nervous system—resting in barracks on the reticular walls of capillaries and sinusoids, making up what is known as the reticulo-endothelial system. Under the stimulating effect of the multiplying plasmodia of malaria they become transformed into active and highly phagocytic cells. They have enormous potentialities of multiplication, regeneration, and repair, and besides their function of direct attack on foreign invaders, they are also the most probable

source of antibodies of various kinds in the development of resistance. The malaria parasites, more than other pathogens, seem to throw the brunt on the phagocytic rather than the antitoxic potencies of these tissues. As Golgi said, the peripheral blood shows only faintly the remarkable changes taking place, for in man, as in monkeys and in birds, the drama goes on in the internal organs. Thomson[1] had occation to examine a number of parturient mothers among the natives of Nyasaland, and he writes that there was a striking contrast between the intensity of the placental infections and the scarcity of parasites in the peripheral blood. The phagocytic picture of the placental smears showed the active part played by the macrophages and leukocytes in controlling *falciparum* infections, and their 'predilection for fully developed or nearly mature schizonts'. Stott[2] and others have occasionally seen the phagocytosis of malaria parasites in the peripheral blood of man in very severe cases of malignant tertian malaria with half the red cells infected and sporulating forms numerous. Both Thomson and Stott speak of the engulfing of living parasites, but Yorke thinks that phagocytes are scavengers of damaged cells, or cells which have been changed by antibodies. Taliaferro merely states that the parasites are removed continuously from the peripheral blood and not only when they are passing from one blood-cell to another, as Bass and Johns once thought.

In the large veins of the periportal connective tissue the number of white cells becomes almost equal to the number of red blood corpuscles, while in the sinuses of the spleen and lymph nodes, when the fixed reticular cells become transformed into macrophages, they accumulate in such masses that Bruetsch[3] refers to them as 'phagocytic tissue', rather than as individual cells.

The first of these great cells to be discovered were the

[1] *Proc. Roy. Soc. Med.* **28**: 391, 6 Dec. 1934.
[2] *Ind. Med. Gaz.* **68** (9): 507, Sept. 1933.
[3] *Am. Jl. Psych.* **12** (1): 19, July 1932; and *Jl. Nerv. & Ment. Dis.* **76** (3): 209, Sept. 1932.

Kupffer cells in the vascular channels of the liver, named after the Munich anatomist who observed them about a hundred years ago. Von Kupffer noticed that, after the cells had taken up particulate material from the blood flowing by them, they lost their hold on the capillaries and came away into the stream, new ones being provided by a proliferation and differentiation of the fixed cells of the reticulo-endothelium. It was difficult to follow and study their activities because of the other types of cell always present in overwhelming numbers in their natural habitat in the liver. Rous and Beard,[1] working at the Rockefeller Institute, have recently discovered that if colloidal iron, which has strongly magnetic properties, be injected into the circulation of a rabbit, the particles are taken up by the cells of the reticulo-endothelial system, including the Kupffer cells. If the liver is washed out after a few days, the great phagocytes containing iron can be separated with an electromagnet from the other cells in the wash water, and if cultivated will live and multiply for at least ten days. The Kupffer cell, seen in pure culture, is of enormous size, varying between forty and a hundred microns in diameter, which actually brings it within the limits of visibility of the naked eye. It is surrounded by an immense enclosing membrane which is remarkable for its stickiness, so that any particle with which it comes in contact adheres tenaciously to its surface. In culture, as in the body, it requires a supporting framework for its growth, such as thin Japanese lens paper, to which it clings, and if torn from its anchorage it soon dies.

The mobilization of such a formidable army takes time, but it proceeds rapidly. Eighteen hours after infection, as Taliaferro has shown, the connective tissue wakes up; the reticulo-endothelial system develops enormous activity, there are mitotic figures in the spleen and its volume increases; the whole phagocytic mechanism is excited, and yet throughout the incubation period the curve of increase of

[1] *Jl. Exper. Med.* **59** (5): 577, May 1934.

the parasites is smooth, and hence the activation of the tissues must just keep pace with parasitic reproduction. At a certain point the defensive tissue finds itself a match for the enemy, and probably, as in other diseases, the destruction products of invaders and defenders alike produce the clinical symptoms characteristic of malaria, the high temperature in turn rendering the leukocytes still more active and effective.

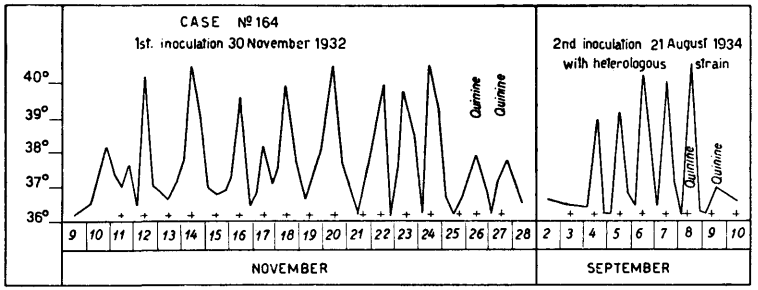
With all this extraordinary activity and acquired efficiency the army is, nevertheless, trained to combat a single foe. From the first access of fever the body begins to acquire resistance, and this, through further paroxysms and relapses or reinoculations with the same strain, can be built into a solid immunity not to be shaken by the most tremendous superinfections. But this state of preparedness is surprisingly and disappointingly specific. The immunized individual may put up an ineffectual defence to a later infection by the *same species* of parasite if obtained from a different source. The two micro-organisms, though quite indistinguishable under the microscope, may actually have so little in common that the phagocytic cells do not recognize the new enemy in spite of its resemblance to the former invader. The body will allow it to obtain a foothold and to multiply enormously before again calling out and re-educating the troops. With each new strain, it seems, the body must go through the same hard experience before it learns to overcome and destroy the parasites, without delay, at the point of entry. We hear a good deal about the 'salting' of new-comers to a malarious region, and Governor Swettenham told Darling that the new civil servants in Singapore were of no use until they had had their fever. Chronic cases certainly do not often come down with pernicious malaria, but in ordinary experience it appears that a person is only really salted to the strains with which he has been infected.

Nevertheless, a certain spread of tolerance cannot be denied, and persons who have once had malaria will never

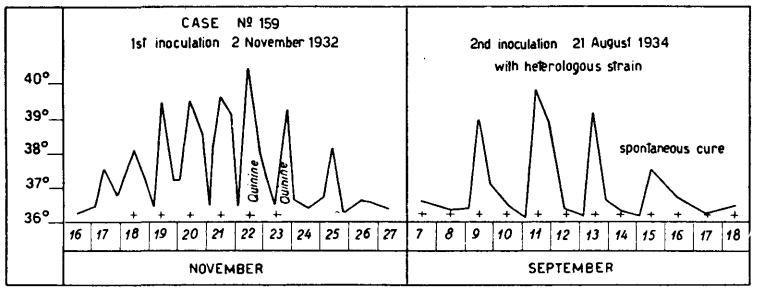
react again in precisely the same way to subsequent infections with the same species of parasite. It even happens occasionally that persons who have had one attack of benign tertian malaria will afterwards prove completely resistant to a different strain altogether. We have maintained several strains at various times in our laboratory from widely separated sources. A number of cases which had been infected with the plasmodium from Madagascar were tried again two years later with a local Italian strain (Fig. 14).[1] Almost all were quite susceptible, as was expected, and yet there were degrees of susceptibility. The curves show that the first case could not muster the slightest resistance, but the second responded to a second infection with a tertian instead of a daily type of fever, as in the first attack. Only one case seemed absolutely immune, although, being a native of southern Italy, previous bouts with malaria cannot be excluded. But when we tried to infect some old Madagascar 'graduates' with the same strain again, we failed completely in almost every case, even after two years. Yet the individuality of the patient was again a factor, for in rare cases the person was unable to oppose a solid resistance, but gave some febrile indication of a partial susceptibility.

While the army of defence is recruited from connective tissue in every part of the body, the spleen seems to have a special function to perform which cannot be assumed by the liver or any other depot of the reticulo-endothelial system. Its removal will promote an attack at once in a monkey which has acquired an apparently unshakable immunity. Effective ability to control the multiplication of parasites seems to be lost with the spleen. The migration of phagocytes into the interior of the spleen, charged with the debris of parasitic destruction and with engulfed red cells containing the living parasites themselves, is one of the causes of the enlargement of that organ, which plays the role of an adsorptive filter. In bird malaria, it is the spleen which

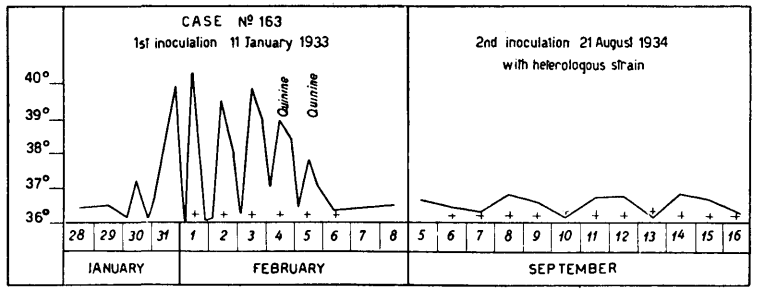
[1] Mosna, E., *Riv. Malariol.* **14**, sec. 1 (2): 121, Mar.–Apr. 1935.



Unaltered receptivity to second strain.



Slight resistance to second strain (tertian paroxysms).



Complete resistance to second strain.

FIG. 14. RESULT OF REINFECTIONS WITH NEW STRAINS OF *P. VIVAX* (*after* Mosna, 1935).
On the days marked +, parasites were found in the blood.

shows the greatest reaction. Sergent tells us that it becomes eighteen times as large as normal. The spleen is (with one exception) the most vascular and expansile organ of the body and easily becomes turgid with blood under stimulation, which explains the acute, soft enlargement which takes

place so rapidly in children. It has been shown in dogs that a spleen can be distended to seven times its volume in a few hours by ligation of the veins and stimulation of the appropriate nerves. It can go down just as rapidly. But the hard chronic spleens are due to multiplication of the macrophages, and the demobilization of these tissue phagocytes is slow. The spleen also picks up and throws upon its midden the overloaded white cells of the blood and the Kupffer cells and other tissue phagocytes which, having slipped their anchors, are brought to it in the blood-stream laden with debris, 'blocked', as the immunologists say, and no longer useful to the army of defence. The enlargement of the spleen is therefore not only a sign of the disease, but a measure of the intensity of the defensive reaction, while its consistency is an indication of the stage of the battle.

The sudden establishment of complete resistance to a plasmodium strain occurs only in birds. In bird malaria there is a crisis accompanied by the wholesale annihilation of plasmodia, leading either to death or to the suppression of all parasites in twenty-four to forty-eight hours, upon which a stage of latency ensues. The host acquires no resistance during the incubation period of the disease, but in the latent period immediately following the crisis the injection of large quantities of parasites causes no attack and they are quickly removed from the blood. This immunity to superinfection may last a long time—in one of Cannon's birds, for 654 days after the acute attack. Why do the phagocytes of a bird with chronic malaria immediately ingest and destroy injected organisms while those of a normal bird do not? Why does superinfection in man find the spleen ready, so that within six hours it can be brought into effective action? It is the result of education and the formation without doubt of an opsonic antibody. Opsonins are immune substances, produced by the presence of foreign bodies in the blood, which seem to direct the activities of the phagocytes toward these bodies. The great macrophages,

with their wide and sticky membrane, develop a selective stickiness for the malarial parasite. If opsonins cannot be found and if in general the serological findings are so meagre in malaria, it is probably due, as Taliaferro suggests, to the localized nature of the tissue reaction, so that in the peripheral blood the antibodies are greatly diluted and cannot be demonstrated in significant quantities by any of our ordinary tests. It is not possible by blood injection from latent cases to transfer the supposed opsonin to another individual. We deduce its presence from its activities. It is formed during the incubation period and it keeps the body constantly on a war footing against this particular enemy. It supplies the special attraction or chemotaxis which is needed to influence the phagocytes to approach and engulf the organisms. The nomadic destroyers are extraordinarily sensitive to this kind of stimulation, once it becomes effective.

But the enemy too is resourceful. It is suppressed but not exterminated. It retires on its base in the marrow of the long bones. Here in the blood-factory itself the parasites seem to be particularly unassailable, whether because the new-born phagocytes are young and inexperienced or because the immature red cells are specially susceptible to infection. Eaton,[1] in fact, has a theory that, even in the blood-stream, the younger a red cell is the more easily it falls victim to the malaria parasite. At all events, here the plasmodium continues to multiply and watchfully to wait. There supervenes then, upon the acute attack, a pause for breath brought about by the temporary supremacy of the defensive reaction of the body—a latent period in which the infecting organism is brought to bay by a painfully acquired capacity to resist on the part of the host.

Latency

The latent period represents a precarious equilibrium between the parasite and what Taliaferro calls 'the killing

[1] *Am. Jl. Trop. Med.* **14** (5): 431, Sept. 1934.

mechanism of the host'. The parasites out of reach go on dividing at the normal rate, but any increase is prevented by the watchful phagocytes. In fact, the parasites are reduced to such a low level that the spleen begins to diminish in size, having not very much to do. This infection-immunity balance is subject at first to irregular wide oscillations before coming to a provisional stability. A case of *falciparum* malaria may recrudesce time after time with only the briefest intermittencies, whereas the curve of *vivax* resistance shows long waves of quite a different order. In any event latency once established may terminate theoretically in one of two ways: cure with eradication of the parasites or an upsetting of the balance followed by a relapse.

I use the word 'theoretically' because we never know when any one is cured. Our only proof is a renewed susceptibility to reinfection by the same strain of parasite (a test impossible of application, of course, in nature), and if it is true that immunity can persist for some time after the disappearance of the last plasmodium, even such evidence would leave us in doubt as to when the event took place. Mühlens[1] reports that even now, seventeen years after the World War, ex-soldiers turn up at the Hamburg Institute complaining of chronic malaria contracted on the Macedonian front, but that for the last seven or eight years he has never once been able to find a parasite or provoke a relapse. James[2] has had much the same experience in England and adds that not all these persons are malingerers by any means, but may be victims of psychoses built up through the continuance of some form of sickness benefit on account of malaria infection. It is pretty well agreed among malariologists that it would be an extraordinary case in which plasmodia could ever be demonstrated in an infection four or five years old. The presumption is that, if an individual passes an entire year without signs or symptoms

[1] *Arch. f. Schiffs- u. Trop.-Hyg.* **39** (2): 74, Feb. 1935.
[2] *Malaria at Home and Abroad* (London, 1920).

of malaria, he may be considered a clinical cure, since experience has shown that he is not apt ever to relapse again. We experience a slight shock, therefore, when Manwell reports two cases of blood-donors who have infected others with quartan malaria after they themselves had been without symptoms which they could recognize for thirty and forty years respectively.

It is not possible to test such cases for absence of parasites by reinoculation with the same plasmodial strain with which they were originally infected, nor may the drastic measures be employed on human beings that are sometimes used on animals to provoke relapse. Knowles and Das Gupta[1] once received a lot of five monkeys of the species *Silenus irus*, which they proceeded to examine for natural infections. One of these was positive for *P. inui* and another showed rare parasites after long search, too few for identification. The three negative monkeys were each given 2 cubic centimetres of normal horse serum, but the resultant protein shock did not produce a relapse. An attempt was then made to infect other monkeys by blood transfers, and this was successful in one case. Still not satisfied that the remaining pair were malaria-free, Knowles and Das Gupta removed their spleens, and each not only developed an attack, but one actually revealed a double infection of *P. inui* and *P. knowlesi*. This illustrates the practical difficulties in the way of proving a human being free from infection.

The suggestion has been made that the body rarely or never succeeds in completely eradicating a malaria infection. We do not know enough about monkeys yet to be sure. Cures are, however, still virtually impossible to prove. Nauck[2] had an infected monkey which after treatment with large doses of atebrin did not relapse, remained free from parasites, and eventually came down with a typical attack upon reinoculation with the homologous strain of the

[1] *Ind. Med. Gaz.* **69** (10): 541, Oct. 1934.
[2] *Arch. f. Schiffs- u. Trop.-Hyg.* **38** (8): 313, Aug. 1934.

malaria organism. It is well known that canaries, after inoculation with malaria, usually remain infected all the rest of their lives, although Sergent reports that occasionally an infected bird after several years may again become susceptible to reinfection. He believes that there is no true immunity in malaria, but only a state of 'premunition' sustained by living parasites in the body.

During a long latency the control of the body over the parasite may relax to such an extent that the peripheral blood becomes thronged with parasites as in a clinical attack, though no symptoms whatever are produced and the infected individual remains completely unaware of the event. Thus he becomes 'an apparently healthy carrier', the sort of person we look for when we take the parasitic index of a population. Important as this phenomenon is to malarial epidemiology, we have no satisfactory explanation of it. Is it a subliminal attack provoking a slight reaction on the part of the host and giving a fillip to the idling machinery of defence? Or has the body acquired two independent kinds of immunity, one to the parasite itself, leading to its corporal destruction, and one neutralizing the pathological effects of its growth and activity upon the host? Perhaps these are 'undamaged' parasites, and hence not phagocytized. Claus Schilling believes that immunization in malaria is a reciprocal reaction between organism and host, in which each is protected from the other as in the ordinary 'carrier' diseases. The truce in malaria must be a little different then from that in other 'carrier' diseases, being transitory and apt to end unexpectedly in a renewal of hostilities.

Whatever the reason, the relative tolerance which the body gains, through a malaria attack, to the presence of parasites in the blood explains the high figures which Ross and Thomson obtained for the fever threshold in the cases which they studied in the hospital at Liverpool. These sailors had contracted their malaria overseas, and all the

attacks studied were relapses. As Boyd has suggested, a high parasitic density on the day of onset is the one important distinction between primary infections and relapses.

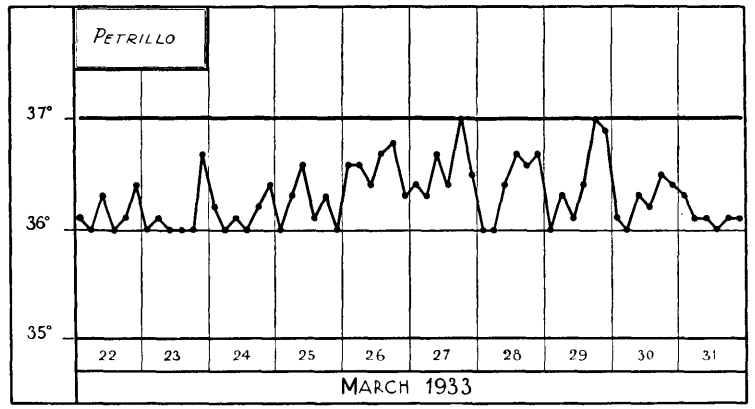


FIG. 15. A SUBLIMINAL ATTACK DURING LATENCY.
Ten days from the temperature chart of an infected person during a long latent period. While the temperature never rises above the normal line (37° C.), the chart gives an impression of mild tertian accesses rising to relative heights on the 27th and 29th of the month and then dying out. No parasites were found.

Relapse

The renewal of the disease signifies a removal of the killing mechanism. It has always been considered of great practical utility to try to determine the various causes which are able on occasion so rapidly and easily to put this defensive mechanism out of action. It has been the general impression that a relapse in malaria may occur at any time in the course of the disease. A patient may hardly have recovered from the primary attack before plunging into a severe recrudescence, or he may enjoy eight or ten months of complete freedom from any subjective symptoms, only to come down again with fever when he has almost forgotten his original infection. Clinicians have always sought for the immediate antecedent causes of relapses, just as we do in food infections and colds. Long ago Caccini compiled

a long list of probable causes of relapse, and to this Ross added several more. These included fatigue, heat, dietetic indiscretions, intercurrent diseases, chilling, drugs, blood-letting, trauma, parturition, and surgical operations. Ross added anxiety, sorrow, shock or fright, alcoholic and other excesses, exposure to the tropical sun, and premature cessation of quinine. This list could be made much longer without adding in any way to our knowledge of the true mechanism of relapse. Recently Eaton has suggested that perhaps very new red blood-cells (reticulocytes) are particularly hospitable to the malaria parasite and so relapses are apt to occur during periods of active blood regeneration, as, for instance, after haemorrhage or ascent to high altitudes. If we consult the lists of Ross and Caccini, it is evident that there should be little periodicity about relapse. The chance occurrence of any number of untoward events may bring about a lowering of resistance at the most irregular intervals, and the rapid multiplication of the expectant parasites.

The different kinds of malaria behave differently with regard to relapses. *Falciparum* malaria, as James[1] has pointed out, is a recrudescing rather than a relapsing infection. There is no undue prolongation of the incubation period so often seen in *vivax* or quartan; no characteristic long latency after the primary attack and no true recurrence at long intervals (Fig. 16). Of quartan relapses we know little more than that which the early malariologists, with their keen faculty of observation and abundant clinical material, have told us. It is a persistent infection with few spontaneous recoveries and long latencies between recurrences. Manson summed up the three species as follows: *P. vivax* is capable of maintaining itself after a single infection for a period of about three years after which it dies out; the quartan parasite may persist for six or seven years, but a single infection of *falciparum* at the most survives from one month to one year.

[1] James, S. P., *et al.*, *Proc. Roy. Soc. Med., Sec. Trop. Dis.* **29**: 27, June 1936.

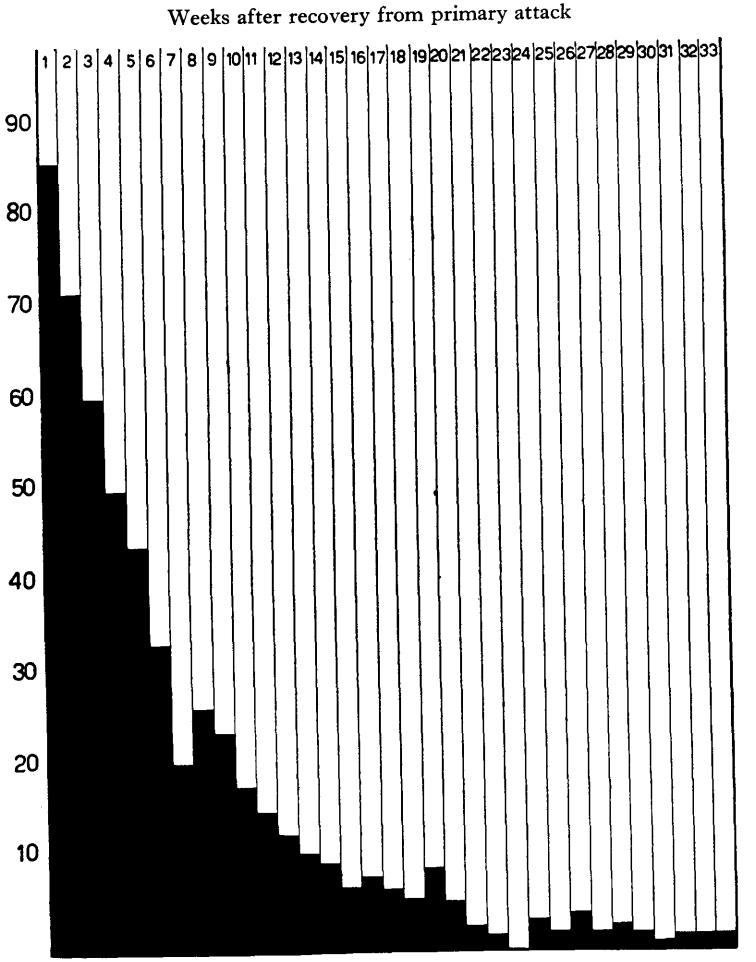


FIG. 16. RELAPSES IN INFECTIONS WITH *P. FALCIPARUM*. *After* James, Nicol, and Shute, *Proc. Roy. Soc. of Med., Sec. of Trop. Dis. & Parasit.* **29**: 27, June 1936.

It is evident then that the persistence of infection and the periodicity of relapse depend a great deal on the type of parasite concerned, and the purely fortuitous and individual occurrences of daily life may have a determining influence only within narrow limits. In *vivax* infections there is a

high uniformity in the percentage of cases which relapse, regardless of locality, social condition, or treatment. A great mass of data has accumulated concerning *vivax* infections the world over, and the experience of almost every one agrees that about 50 per cent. of benign tertian cases relapse on the average everywhere. We have a considerable experience now with induced infections of *vivax* malaria which are protected from some of the variables affecting cases in nature. They frequently receive no treatment whatever but recover spontaneously, and they remain indefinitely in hospital, leading a sheltered existence protected from most of the contingencies mentioned on Caccini's list of the causes of relapse. Nevertheless, in Boyd's series 60 per cent. showed some further manifestation of disease after spontaneous recovery. This would surely indicate some factor at work in the production of relapses other than pure accident.

There is a certain regularity about the recurrence of *vivax* infections in the spring. This leads to an accumulation of cases early in the year, usually referred to as the spring 'peak' of malaria, to be contrasted with the autumn peak, due as a rule to new infections. Malariologists often inoculate themselves and not infrequently their families and friends in the interests of science. Before therapeutic malaria furnished an abundance of volunteers, these accurately observed cases served as valuable touchstones of fact with which to compare the less complete observations in nature. In 1917 Roubaud infected himself with benign tertian malaria on 14 September, going down with a sharp attack eight days later. He took alternating doses of 1 and 2 grammes of quinine daily, which did not prevent an immediate recrudescence on 28 September. He pursued the same treatment for another week and took no more quinine till the recurrence, seven months later, on 17 April. One more relapse on 2 July and he was done with the acute episodes of his infection. This recalls the classic case of Thorburn

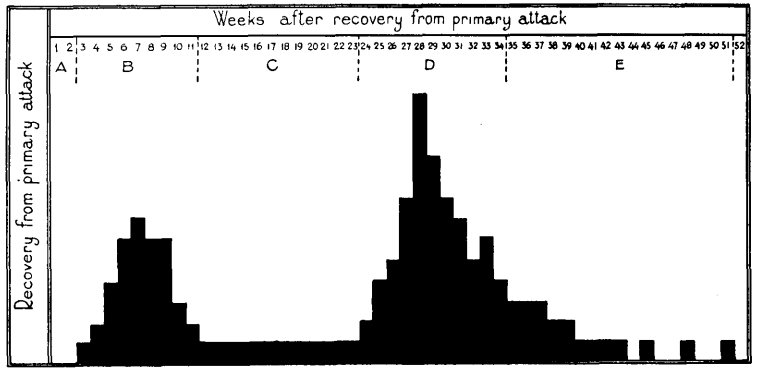
Manson,[1] who was bitten in London, on 29 August 1900, by mosquitoes brought from Rome. He had his first symptoms on 13 September and his first recurrence nine months after his infection, on 1 June 1901.

Such relapses have been rather plausibly assigned to seasonal influences, although not necessarily to weather, for Manwell[2] has reported the tendency of relapses in birds to occur at the same season but independently of climate or other environmental conditions, which in the laboratory are constant. Therapeutic malaria affords us almost the same opportunities to observe considerable numbers of infected patients, protected from the minor accidents of life and weather. They spend much of the time in bed and most of it within doors, and pursue an even tenor of existence, sheltered and well nourished. Under such conditions James noticed a characteristic uniformity emerging from the statistics of his protracted cases of induced tertian infected with the Madagascar strain. This underlying rhythm might easily be obscured by fortuitous circumstances in individual patients, but it appeared in any group of cases, not necessarily very large. By charting the cases for a period of a year and bringing the inoculation dates together in one line, there was an evident similarity in the chronic course of the disease. For instance, of 150 cases infected by mosquitoes, 37 recrudesced within 8 weeks, 12 relapsed between 8 and 24 weeks, and 30 recurred after 24 weeks, principally between the thirtieth and fortieth week. In all, 29 or 53 per cent. of the cases had a return of fever. 'It is evident', James has written, 'that a peculiar character of benign tertian is liability to a return of fever and parasites at an interval of between thirty and forty weeks after the date of first infection by mosquitoes.'

The graph representing the relapses of these cases (Fig. 17) shows that, with a certain variation, one case of benign

[1] Quoted by Ross, R., *The Prevention of Malaria* (London, 1910), p. 81.
[2] *Am. Jl. Hyg.* **9** (2): 308, Mar. 1929.

tertian infected with a given strain of *vivax* behaves very much like another in patients under fairly constant and equable conditions. Thus the peak of tertian in spring may not be due to any special climatic or other environmental condition peculiar to that season, but may result from the fact that March, April, and May are between thirty and



From the Quarterly Bulletin of the Health Organization of the League of Nations, Vol. II, N°2, p. 229.

FIG. 17. RELAPSES IN INFECTIONS WITH *P. VIVAX*.
Based on 150 cases of induced malaria.
(*After* James.)

forty weeks after the season of mass-infection of the population in the preceding autumn. The natural course of a malarial infection would, according to this theory, reflect the inherent periodicity of the parasite itself. After recovery from the primary attack there is a pause about equal, as Caccini noted years ago, to the incubation period of the disease. Then follows a period of about two months when the patient may have one or more recrudescences. Weathering these, he may expect a long latency, during which his developed mechanism of defence will be able to keep the natural increase of the parasites in check. Finally, seven to ten months after the primary attack, will come a recurrence of the disease with successive recrudescences and further relapses, until he is finally rid of his infection.

So much then for a single strain of *vivax* under laboratory

conditions. Inherent periodicity is more evident than the effect of chance incidents. But in nature the parasitic rhythm tends to be obscured by a variety of other factors. The usual history of a relapse does not immediately suggest the dominant role either of external influences or of inherent periodicity. The sudden removal or paralysis of the killing mechanism is the striking thing. What is the incubation period of relapse? Where have the parasites been that so suddenly swarm into the peripheral blood almost immediately after the so-called exciting cause of the relapse? Yorke places the responsibility for relapse upon the individuality of the patient and his ability to develop and retain an active immune body.

Individuals vary greatly in their defensive powers. Some are refractory to the original infection, some are almost indefinitely receptive, unable to accumulate resistance to the disease. In Portotorres (Sardinia), our earliest anti-malaria station, after the first two years of successful control it was always the same group of unfortunates who presented themselves time after time at the dispensary for treatment of relapse. Every one has had the same experience. Hill mentions a boy of thirteen at Campo Lugar in Spain, who was treated frequently as a chronic malaria patient in 1931, the first year of the station. He had twenty examinations during the course of 1932, of which ten were positive, although he consumed 40 grammes of quinine, and anti-larval work had greatly reduced the chances of reinfection. The infection still persisted at the end of the year. These individual differences in susceptibility often reveal themselves strikingly in children of the same family, equally exposed to infection.

Such patients used to be called resistant to quinine, though it is undoubtedly an immunity phenomenon, since malaria parasites, as far as we know, never become quinine-fast, in the sense that trypanosomes become resistant to arsenic, remaining in the peripheral blood unaffected by

treatment. In this organism, as Yorke and Murgatroyd have shown, repeated non-sterilizing arsenical treatments produce a true mutation. A new race of trypanosomes is formed which through succeeding generations without contact with arsenic for many years, and even after several passages through the insect host, remains just as tolerant as the original arsenic-fast strain. Plasmodia, on the other hand, are quickly driven from the circulation by quinine, and, if they reappear at once, it is because are they invulnerable to the killing mechanism of the body but not to the drug. Thus the permanent effect of treatment is dependent on the immunity factor.

But the gradual waning of bodily immunity is not completely satisfactory as an explanation of relapse. Successive relapses become not more severe but less severe as time passes, until clinical attacks cease entirely, although the infection remains alive, coming occasionally to the surface as 'parasitic relapses'. After a short period of years even these fade away and the plasmodia are never seen again. Still the patient may be resistant to superinfections. Is this a cure with continued resistance or is it a permanent stalemate between parasite and its host? We have no means of knowing, but we suspect that most malaria infections pass through a latent period of indefinite duration before they are ultimately extinguished. In other diseases, as for example diphtheria, the infectious blood gradually becomes sterile during the long period without symptoms. In such latent infections the body must be continually reacting to antigenic substances by the production of new antibodies, a process called latent immunization. Such a process is certainly suggested by the picture of a malaria infection slowly vanishing away.

There is a fourth factor which has recently been implicated in the frequency of relapse: namely, the relapsing character of certain plasmodial strains. It will be recalled that, among the monkey strains which Sinton isolated, K 4

was different from the rest in its persistent tendency to relapse, and relapse severely. At the other extreme we have those very common benign tertian infections of northern Europe in which even the primary attack is completely suppressed. The incubation period passes without interruption into a long latent period terminated seven or eight months later by a relapse, which is the first clinical manifestation of the disease. It is even possible that some infected persons reach a permanent cure without any obvious attack at all, as sometimes happens in dengue and typhus fever, and other diseases in which persons become infective without any clinical symptoms, and then eventually cease to be carriers again. This primary latency or prolonged incubation may occur in benign tertian anywhere, and isolated cases are continually being reported from all over the world, but it is the characteristic type of malaria in Holland, northern Germany, and England. Here summer and autumn infections in nature cause an annual outbreak each spring, and it would not be illogical to suppose that season had something to do with the matter, were it not for the fact that under experimental conditions it appears to bear no relation to the seasons of the year. It seems also that, the fewer the sporozoites injected, the oftener the incubation passes into latency without fever or parasites that can be found. This is another reason for regarding with suspicion some of the results reported from laboratory infections. Almost always the dosage of infection in the laboratory is larger than that in nature. Nevertheless, initial latency seems a character which belongs particularly to certain strains.

We have then as causes of relapse either environmental influences, oscillation in individual defensive powers, or an inherent periodicity of the parasite with varying tendencies in different strains. We cannot yet discard any of these, and probably all enter the picture to one degree or another. The immune factor and its gradual diminution with the lapse of time is clearly fundamental.

Gametocytes and Immunity

Gametocytes are the emigrant forms of the malaria parasite which, transferred by mosquitoes to healthy individuals, cause the spread of the disease. They appear in the blood mingled with ordinary forms (trophozoites), which grow, divide, and cause the fever. We really know very little about them, when or where or how they are produced in the body, yet these are the forms which to the epidemiologist are by far the most important of all. Owing to their peculiar structure and behaviour, they had been discovered and distinguished from the trophozoites long before the transmission of malaria by mosquitoes had been proved. Manson saw the flagella which a certain proportion of the peculiar bodies produced, and thought they might be the continuing forms in the mosquito. He spoke about the matter to Ross as early as 1894, but for some reason Ross did not pursue the subject far enough, although he observed the exflagellation in the stomach of a mosquito in 1895. It was reserved for an American, two years later, to wonder why only half the forms flagellated, to observe that there was an eventual conjugation between the flagellate and the other forms, and to reason that this was undoubtedly a sexual process. This was communicated in a paper read before the British Society for the Advancement of Science on 24 August 1897. In a letter to me some years ago MacCallum recalled the story of his youthful discovery.

'I pursued crows in the open', he wrote, 'for part of one summer but could never shoot one without killing it, although I could recognize the sick crows by their ruffled plumage, their queer croak, and their quiet attitude on the branch of a tree. They were watched over by other crows who called to them from on high. I heard one day that some boy about three miles up the river had two pet crows, and I took slides and covers and rode there on a bicycle, bringing back a drop of blood from each. In one of these I saw a form, the vermiculus, which we had never seen before, and recognized the fact that my slow progress on the bicycle was the only thing which could account for such a difference. I went back and brought the crows and the next morning a fresh drop of blood showed the ordinary malarial parasites. I knew then that I must watch a drop of blood on the coverslip for at least half an hour before the new forms would appear, and finally after many days I saw the whole thing and recognized its significance largely on the basis of the conjugation of spirogyra which takes place only when that alga is put under unfavourable conditions.'

Unfavourable conditions, however, seem to have very little to do with the formation of gametocytes in the human body. At one time it was reported by several observers that short treatments with quinine increased the number of gametocytes in the peripheral blood. This was disquieting, for any form of treatment tending to increase their numbers might render the case a good infector of mosquitoes and a danger to the community. Clark[1] and others observed that plantation labourers treated 'insufficiently' in hospitals and dispensaries, and discharged in a week or ten days, often went home without clinical symptoms but with a high density of gametocytes in the peripheral blood. In fact, these treated individuals had a much higher gametocyte rate than the natives of near-by villages who were equally malarious and received practically no treatment. It was later found that the quinine did not stimulate the production of gametocytes, but that these were the natural sequelae of an acute attack of malaria and that, in the case of crescents, even a protracted treatment would not prevent their appearance. That the villagers had fewer gametocytes than the plantation labourers seemed actually to be due to a higher intensity of infection.

It used to be thought that the parasite, as soon as it finds itself in adverse circumstances owing to the increase in the defensive powers of the host, begins the manufacture of gametocytes by means of which it can secure its transmission to another host. Schüffner[2] (1919) and Christophers[3]

[1] *Am. Jl. Trop. Med.* **7** (1): 15, Jan. 1927.
[2] *Meded. Burg. Geneesk. Dienst. Ned.-Ind.*, No. 9: 20, 1919.
[3] *Ind. Jl. Med. Res.* **12** (2): 273, Oct. 1924.

(1924), in opposition to the prevailing idea at that and later times, proved that the formation of crescents is not associated with immunization but is reduced during this process. Gametocytes are, in fact, characteristic of primary attacks and of attacks in babies, and they are correspondingly rare in chronic cases with a high immunity. It is not even certain that the production of gametocytes does not begin at once and accompany without retardation that of the asexual forms. It is true that the division forms appear first and then the gametocytes a few days later, but, as Yorke says, it is not necessary to infer that the trophozoites are actually present in the blood before the gametocytes. With *vivax* the former almost invariably outnumber the latter, consequently they will be the first discovered at a time when the blood films contain few parasites. 'Patients infected with benign tertian', says Boyd, 'are practically speaking infectious for mosquitoes from the onset.'

Gametocyte production is more constant and abundant during primary attacks than recurrences. However, the sexual forms are usually found much earlier in relapses than in primary attacks, which means that both gametocytes and trophozoites rapidly attain such numbers as to put themselves almost simultaneously within reach of microscopic search. To the body, however, they are independent organisms. In the tropics, where immunity is more rapidly and permanently established in the first decade of life than in temperate climates, it is usual to find the gametocytes under more stringent control than the trophozoites. Thomson found among the native children of Nyasaland that while the parasites of *P. vivax* and *P. malariae* had practically disappeared from the blood by the age of nine, all the children continued to show the ring forms of *P. falciparum*. No gametocytes of any kind, however, were to be found after that age (Fig. 18).

In therapeutic malaria, after many passages by direct blood inoculation, gametocytes sometimes cease to appear.

It would seem almost as though the ability to produce gametocytes was a genetic character which might be lost in the prolonged deprivation of the sexual cycle. Huff and Gambrel received a strain of *P. cathemerium* from Rome

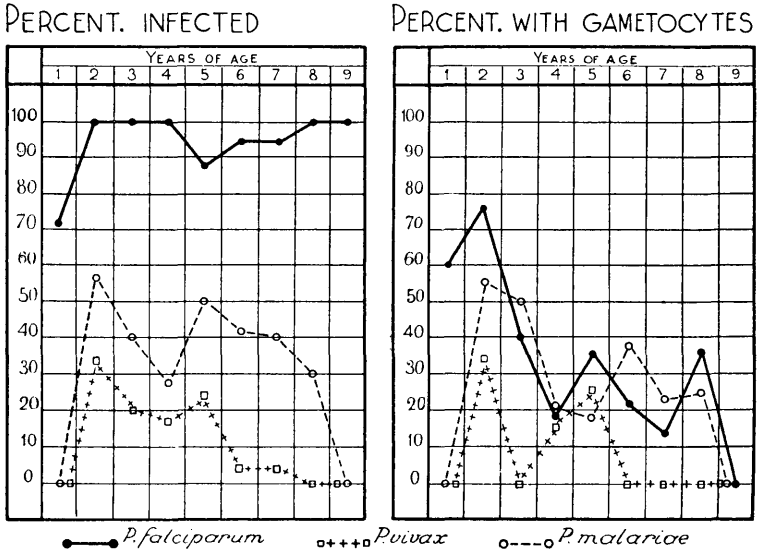


FIG. 18. PERCENTAGE OF CHILDREN INFECTED, AND PERCENTAGE WITH GAMETOCYTES, ACCORDING TO AGE. (103 NATIVE CHILDREN IN NYASALAND.)
(*After* Thomson, *Proc. Roy. Soc. Med.* **28**: 391.)

which, after seven months of intravenous passage, suddenly ceased to produce gametocytes, nor did they ever appear after subsequent inoculations. With the loss of ability to produce gametocytes the atypical strain lost almost all trace of periodicity. However, the original strain transmitted from a latent bird before the gametocytes were lost has continued to produce them normally ever since.

The presence of gametocytes in the circulating blood is not in itself an indication that the patient will infect a mosquito. Good infectors are rare, and James has pointed out that it is the quality and not the number of the gametocytes which seems to be important. But what this quality is, and

why only a few individuals become and remain gametocyte carriers over long periods of time, we are not in a position to understand.

The more we try to peer behind the scenes in the malaria drama the more we perceive that the immune mechanism succeeds to a large extent in restricting and modifying the activities of the parasite in the human body. The clinical, pathological, and immunological features of any case of malaria infection are always the resultant of two opposing factors: the particular strain of the parasite with its assortment of inherent biological characters, and the defensive powers of the host, which vary widely from individual to individual. The acute stage ends when these factors come into dynamic equilibrium, and upon the nature and stability of this equilibrium depend not only the relapse history and eventual recovery of the case, but also the conditions which govern the transmission of the infection in nature to other individuals.

Mixed Infections

It is evident that in a zone of intense transmission, in which all three malaria species are present with no cross-immunity between them, mixed infections in the population will be the rule rather than the exception. Nevertheless, the blood indices of such a population in our experience have shown only 1 or 2 per cent. of such mixtures, although Knowles and Senior-White state that by careful and repeated examinations this percentage can be greatly increased. A mixed infection, however, is not a simple combination of two or more parasites in the same patient. There is obviously some sort of competition between them, ending in the domination of one form to the virtual exclusion of the others from the peripheral blood. In what we now speak of as the early days of monkey experimentation (it was in 1932) Knowles and Das Gupta were conserving a strain of *P. inui*, a newly-found parasite of the monkey *Silenus irus*, by

passage through a *rhesus* monkey, a species uninfected in nature. They were astonished to find that the plasmodium took on quite a different appearance and character in the new host. Behaving much like *vivax* in the original monkey it greatly resembled *falciparum* in the other. This was a new and disconcerting onslaught on the much battered unicity theory, which every one thought had been sunk for good by the findings in therapeutic malaria. It was at first believed that a change in the species of the host had wrought a profound transformation in the parasite. A year or two later Sinton and Mulligan found the new form as a natural infection in an *irus* monkey, and named it *P. knowlesi*. They showed conclusively that Knowles and Das Gupta must have been dealing with a mixed infection in the first place. In *S. irus*, *knowlesi* was so completely submerged by *inui* that it was never found, but when both were transferred to a non-immune *rhesus* monkey *knowlesi* was able immediately to dominate the other parasite. Knowles has since shown how extremely difficult it is to establish by microscopic examination the presence of a suspected latent infection, and yet the frequently successful inoculation test (isodiagnosis) shows that the suppressed form is not absent but only rare in the peripheral blood. Thus in our laboratory the attempt to transfer a strain of *vivax* from a patient whose blood had never shown anything but this organism resulted in a *falciparum* infection in the recipient host.

The species which predominates depends on the immune state of the individual at the time of examination, and, as Sinton suggests, treatment may in some cases exert a differential influence on the two forms. In the acute stage of infection, *falciparum* usually dominates *vivax*, and in adults in hyperendemic areas *vivax* may disappear entirely from the blood picture. In Posada,[1] a very malarious village of Sardinia, we rarely find *vivax* in blood specimens from

[1] Missiroli, A., *Riv. Malariol.* **11** (1): 1, Jan.–Feb. 1932.

individuals over nineteen, but it is present in the anophelines in the same amount as *falciparum*, for, as Fig. 28 on p. 218 shows, *vivax* infection is very common in infants, amounting to half of all the positive findings. In Sardinia, therefore, benign tertian may be called a children's disease.

As is well known, there is also a seasonal influence affecting the blood picture. At any rate, it is a common experience to find the same individual infected with *falciparum* in the autumn and with *vivax* in the spring, although there has been no opportunity for infection in the interval. This is most easily shown by examining a single group of individuals from time to time throughout the year. Barber and Komp[1] found the spring predominance of *vivax* and the autumn predominance of *falciparum* to be striking in the white race in the southern United States, but not noticeable in the black. Of fifty-one children examined throughout the year twenty-three varied in type, and during the winter only two of eleven cases remained constant. M. C. Balfour[2] examined a group of 112 children every month in a Greek village in the Peloponnesus, and of these 45 per cent. proved to have both *vivax* and *falciparum* at some time, yet there were not more than three mixed infections found in one month. The number with parasites increased from 7 per cent. in February to a maximum of 45 per cent. in October, and 85 per cent. of the children were positive at one or more of the examinations.

It is not likely that in such a test twelve examinations will reveal all the mixed infections. It is probable that infection with both parasites in a hyperendemic area is inevitable sooner or later, and that the blood index at any given moment is a highly complex resultant of many factors, in which the differences between *P. vivax* and *P. falciparum* with respect to immunity, latency, duration of infection, and gametocyte production play more of a role than season. In fact the

[1] *U.S. Pub. Hlth. Repts.* **44** (34): 2048, 23 Aug. 1929.
[2] *Am. Jl. Trop. Med.* **15** (3): 301, May 1935.

principal climatic influence would seem to be the negative one of a long winter pause in temperate zones, during which transmission is stopped and *falciparum* infections allowed to clear up.

The question of seasonal influences will come up again to trouble us. I would only insist here that the great quantity of mixed infections is not ordinarily revealed by our indices, and that certain forms are recessive or suppressed to such an extent that we never gain a fair idea of their frequency. For instance, it has been the tradition to believe that *P. malariae*, except in certain endemic foci of the world, is relatively rare. But this, too, may be merely a question of domination by other parasitic types in certain regions. It is evident that in a succession of mild years in an endemic zone *falciparum* infections will, to a great extent, recover, while *vivax* will be much reduced. It might be expected that such a persistent infection as quartan, lasting for six or seven years, would if present outlast the others and appear in relatively greater proportion in the blood indices of the population. This, in fact, seems to be the case. On a survey of Greece, conducted by Balfour[1] in 1934, 8,209 blood specimens were secured, of which 16 per cent. were positive. The proportionate representation of the different species of plasmodium was surprising, in view of the fact that in years of high transmission quartan is a rare parasite in Greece. The examination showed that 34 per cent. were *vivax*, 33 per cent. *falciparum*, and 31 per cent. *malariae*. Thus after several very mild years the three parasites are seen to be fairly evenly distributed in the population. Five per cent. of all examined had quartan, and we may conclude that the same percentage is maintained in other years, but a high inoculation rate of *vivax* and *falciparum* leads to the dominance of one or other of the more common parasites to the practical exclusion of *malariae* from the blood picture for years on end.

[1] *Riv. Malariol.* **15**, sec. 1 (2): 114, Mar.–Apr. 1936.

Malaria under Natural Conditions

If we consider the picture as a whole, the power to remain latent would seem to be the principal characteristic and defence of benign tertian and quartan malaria. It is the outward expression of a stalemate between infection and immunity. It is a protection to the parasite, which has thus found a method of escaping the action of the killing mechanism until such time as that becomes sufficiently feeble to be overthrown. It is the natural protection of the individual, who is able to repair the damages of the acute attack. It is the natural protection of the community against destruction by malaria—indeed, until 1632 it was the only protection human beings had. A balance must always be struck in nature between a parasite and its host. The most successful parasitisms are those which do not disturb too profoundly the normal life of the host; and malaria is one of the most successful of all parasitisms, since through vast lapses of time the attack has developed a counter-resistance which can only check but not destroy it.

Under natural conditions and a high inoculation rate, as among the sparrows of Rome which are almost invariably infected with at least two species of malaria parasite, tolerance must be acquired at a very early age, at the cost probably of a high infant mortality. But the reproduction rate of the sparrows has for ages discounted this loss and is sufficient on the average to maintain the population at the level permitted by its enemies and its food supply. Civilized man is the only animal able to 'multiply upon the earth'. All other species have long ago reached a balance in nature oscillating about a long-time average which changes only with the greatest deliberation in one sense or another.

Sinton has imagined the natural epidemiological situation in a monkey population of the tropics. The communal habits and lack of clothing or protection at night will facilitate infection, while recovery is entirely dependent on the natural defences of the body. The development of immunity will be gradual, the carriers common among the younger animals. The conditions will be similar to those in some remote African or Indian village where treatment is not available. The young will show clinical symptoms and high parasite and gametocyte rates, but clinical manifestations in the adults will be rare and parasites scanty. One plasmodial species bestows no immunity against another, resulting in mixed infections and a composite immunity.

It is likely that among the lower animals there is a racial immunity as well as an acquired immunity which enables them to live almost happily and normally in the presence of malaria. In human beings this is only found in effective degree among the negroes, an indication of the African origin of malaria. Boyd,[1] in his Florida station, never encountered an unsusceptible white patient, though he often failed to infect negroes with *P. vivax*. The resistance of the blacks is to the clinical effects of the organism rather than to the infection itself. At Lagos, Barber[2] found 100 per cent. of the blacks infected after the first year of life. Children suffered somewhat from repeated attacks; young adults in their twenties complained from time to time of vague indispositions which might keep them from work for half a day; those over thirty showed few signs of their latent infections. Early British colonists thought malaria a disease of the whites alone, as was once the opinion about yellow fever. It is possible, of course, that even racial immunity may be limited to local strains of parasites. Van Nitsen[3] describes the relatively high immunity of the local natives in the mining camps of Haut Katanga, but says that natives of Ruanda-Urundi when they come to Katanga are very susceptible to malaria and have attacks comparable to those of

[1] *Am. Jl. Hyg.* **18** (2): 485, Sept. 1933.
[2] *Ann. Trop. Med. & Paras.* **25** (3–4): 461, Dec. 1931.
[3] *Brux. Méd.* **11** (2): 31, 8 Nov.; and (3): 67, 15 Nov. 1931.

Europeans. The acclimatization of these immigrant blacks takes about three years.

The negroes carried much of this natural tolerance with them to America, together perhaps with their own strains of plasmodium. The protection is not proof against infection, however. In the schools of Florida, Griffitts[1] found 10 per cent. of the negro children with parasites but only 4 per cent. of the whites. Nevertheless, while the negroes usually represent the focus of infection in a southern American community, they themselves suffer much less than the whites from the disease. Boyd has found in malaria therapy that negroes usually exhibit a high degree of tolerance to *P. vivax*. In most individuals the resistance seems to be absolute, but occasionally it is found to be only relatively high in comparison with that shown by the whites. Even negro children show an immunity which must be racial in origin. To *P. falciparum* infections negroes show very little natural resistance.

Other races in the tropics do not escape so easily. Malays, as Schüffner[2] and others report, acquire immunity at the cost of much illness. As adults they retain large spleens, though they have low parasite rates. Their immunity is an acquired one, quite different from the natural tolerance of the blacks. The height and constancy of such an immunity depends upon the inoculation rate. It is like sunburn; only continued and frequent exposure will maintain a high level of tolerance. It is thus more than probable that in hyperendemic areas the greatest amount of sickness may not occur at the maximum anopheline densities.

The classic description of the height to which acquired immunity can be pushed among the natives of India has been given by Christophers.[3] Children under five, half the time, had more than 5,000 parasites per cubic millimetre of

[1] *South. Med. Jl.* **27** (5, 6, & 7), May–July 1934.
[2] *Ctbl. f. Bakt. Abt. 1 Orig.* **125** (1–2): 1, 6 July 1932.
[3] *Ind. Jl. Med. Res.* **12** (2): 273, Oct. 1924.

blood. They suffered from an almost continuous attack, lasting two years. The percentage infected was the same in the higher age-groups, but the infection was characterized by low severity, restricted numerical prevalence of parasites in the blood, and few symptoms. Malcolm Watson has raised the question as to whether some Indian races, like those in the Jaypur Hills, may not have a true racial tolerance, since even the children look healthy though they carry a high parasite rate. Sergent has described a great natural resistance on the part of the Arabs of North Africa, a white race. The infection must be of great antiquity to produce such a result.

As we go northward man seems to have retained less and less of the natural immunity he once enjoyed as a denizen of the tropics, if humankind originated there, as some believe. Still, as we have seen, he does possess a natural power to inhibit to a considerable extent the multiplication in his blood of a parasite with which he has never been in contact before. This is not sufficient as a rule to abort the attack, but it probably saves his life. A few fortunate individuals are refractory to all but the severest inoculations. Perhaps this power is a residue of that which in aboriginal man enabled him, unprotected and untreated, to endure without too much discomfort or disability a parasitism which now often paralyses his activities and renders great areas of the earth uninhabitable.

To this natural defence man can add an acquired resistance capable of reaching great heights of effectiveness. This can accomplish more at present than any therapeutic intervention at our disposal, although always a hard-won possession. When completely developed it may not be able to destroy sporozoites, but it can reduce asexual multiplication to a subclinical level, and remove the gametocytes from the blood. There are two weak points in our armour, both arising from nothing else than our temperate climate. The winter pause and the wide

variations in our summer rainfall and temperature interrupt for long periods or render inconstant the rate of malaria transmission, and on this depends the strength of our resistance. Our defences crumble about us inevitably through the winter, and we are in the unfortunate position of a besieged colony inside a broken wall which cannot be restored until an attack is launched against it. Secondly, the children of temperate zones cannot acquire their maximum resistance until twelve or fourteen years of age, and it is they who start the annual epidemic wave in each locality which, without their help, might not achieve in the short northern season that crushing violence with which in the sub-tropics it breaks upon the people in the autumn of the year.

It is the children, of course, who bear the brunt of the disease. In very highly endemic centres the amount of sickness is greatly reduced in comparison with epidemic areas. Students coming from Spain to Sardinia or the Balkans often get the impression that the epidemic malaria in Spain is more severe because the attacks present the classic picture of chills and high fever and cause much loss of time. In a Sardinian town, on the other hand, people rarely go to bed on account of malaria. Infants are often acutely ill, but adults complain principally of a low fever which comes in the evening when they are tired from their work in the fields. The winter spleen rate, however, in Spain would be nearly zero, while in Sardinia it would rarely sink below 50 per cent. There would be a significant difference in anaemia, mortality rates, and other measurable constituents of the 'general health'.

One gets the impression, in fact, that human beings of the white race, unless they live in great aggregations, suffer rather more than the lower animals from the parasitism of malaria. In temperate climates *vivax*, the prevailing species, encounters a stronger and more rapidly constituted opposition than *falciparum*, but the latter, being a more acute

infection, suffers the enormous handicap of being unable in a large percentage of cases to survive the winter. Quartan, for whatever reason, is not usually a factor of importance in Europe. The plasmodia, then, are not as efficient as in the tropics. Nevertheless, there are great sub-tropical populations of the Mediterranean basin and elsewhere which cannot under modern conditions live in a state of natural balance with this parasite on any level which will permit them the life of normal well-being to which they are entitled. As General Cumming once said, 'malaria has the disastrous effect of permitting human existence while precluding the possibility of human health or happiness'. There is no middle way for civilized man of the white race. The requisite minimum of freedom from infection which will permit happiness and progress can only be secured by an effective and permanent interruption of the transmission of malaria.

VII

TREATMENT IN THEORY AND PRACTICE

The art of healing has no more solid basis than experience.
CELSUS (2nd century A.D.).

THE report on 'The Therapeutics of Malaria' by the Malaria Commission of the League of Nations[1] would have had a better reception had its title been less comprehensive. Much of the criticism was aroused by the fact that it came to too many general conclusions on the basis of results obtained in laboratory cases. It was observed that the laboratory cases were drawn from a hospitalized population of adults, sheltered and well nourished, but in an advanced stage of syphilitic infection, so that even benign tertian malaria caused a mortality of over 10 per cent.; and that the experiments had to do with only one or two strains of the malaria parasite inoculated in much larger doses than would ever be likely in nature. The malaria with which the health officer has to deal, on the other hand, consists of mixed infections of all species and of an unknown number of strains of plasmodium in a population containing many children, all exposed to continual reinfection and the vicissitudes of everyday life.

This offers no ground, of course, for criticism of laboratory experiments in therapeutics. Until the present method of malaria therapy enabled us to keep pure strains of the malaria organism in stock and to use non-immune sequestered individuals for clinical subjects, our knowledge of treatment was wholly empirical, confused, and unreliable. It is virtually impossible under natural conditions of endemic malaria to 'claustrate the experiment', as Sir Almroth Wright puts it—that is, to isolate the problem as in a test-tube and study one variable at a time in an environment in which everything else is kept constant. In nature we can do no more than select two situations as nearly identical as can be found, and introduce something new into one of them. They commonly turn out to be extraordinarily complicated and not very much alike to begin with; and they tend in unexpected ways to become less and less alike as the experiment progresses. We then try to measure every changing phenomenon which comes under our observation, striving by correlation to connect it with its more obvious causes, calculating probable errors, correcting for unexpected influences, and weighting the results according to the original or developed differences between the experiment and its control. If we do this very carefully on a sufficient scale, without too many unknowns, we often obtain important information of permanent value. Much of our knowledge of anti-malaria measures has been gained in this laborious and uncertain way. But, as regards the therapeutics of malaria, it has led to that incredible mass of conflicting and immeasurable data known to the despairing research student as the literature on treatment.

Quinine, for example, is a drug which physicians have used for three hundred years without coming to any consensus of opinion as to proper dosage, method of administration, length of treatment, pharmacological action, effective results, or prophylactic value, either individually or socially. The Malaria Commission, after investigating the use of quinine in different countries, reported in 1924 that 'no uniformity was found in the actual mode of treatment employed', and might have added that there was even less agreement as to its action and efficacy. In the ten years which have now passed, the laboratory has done a great deal to bring order into this chaos.

It is now clear that we were expecting far too much of quinine. There are certain things which it cannot do, and these constitutional defects were first incontestably revealed in the treatment of general paralysis. They were not to be

[1] *Quart. Bull. Hlth. Org. L.o.N.* 2 (2): 105, June 1933.

corrected by increasing the dose or lengthening the treatment. Quinine simply does not kill the sporozoites injected by the mosquito and so cannot prevent infection. It appears to be useless during the incubation period or when the disease is latent, for some clinical reaction on the part of the host seems to be necessary to render it effective. It cannot sterilize the sexual forms of *falciparum*, so that cases under treatment continue to infect mosquitoes and remain a source of danger to the community. Finally, no intensification of treatment will result in the radical cure of more than a certain percentage of infected persons. There is always a large group of cases, in other words, which will inevitably relapse. It is even a question whether quinine shortens the natural duration of the malarial infections in susceptible people. We are told that it may lengthen it appreciably, if it is true that quinine checks the growing immunity of the body to the parasite. What it can do is to interrupt the acute attack. That alone, for the lives and the suffering it has saved, will always entitle it to a medal of honour. We have only to consider the serious plight the world was in before the discovery of quinine. If at any time it has fallen into disrepute, it is because we were reluctant to acknowledge its limitations and were always hopefully attempting to turn it to preventive ends.

This does not mean that every one is in agreement on it even yet. The question of the value of prophylactic quinine is a very live one. It is taken daily by thousands of persons in tropical countries (and even nearer home) on the advice and sometimes the compulsion of Colonial Governments. We know very well that the drug will not kill sporozoites, but that does not by any means decide the matter. If quinine does not prevent infection it can suppress the clinical symptoms or render them of little consequence, at least for many months. As a typical example we may cite one of James's[1] experimental cases who received a daily dose

[1] *L.o.N. Hlth. Org. C.H./Mal.*/191, Geneva, 3 Feb. 1933.

of 30 centigrammes for five weeks, during which time the patient was infected and reinfected three times each week by mosquitoes. While the patient was actually taking the daily dose, from 15 August to 20 September, she had only one attack of fever, which was suppressed within four days. Shortly after cessation of the daily dose, however, there was a severe attack with nine paroxysms. The conclusion is that a daily dose of 30 centigrammes (5 grains) is not quite sufficient as a clinical prophylactic where transmission is intense and that its action ceases as soon as it is discontinued; 40 centigrammes would be more effective though not more lasting. Other experiments showed that weekly or semi-weekly doses were of little use. Many people will prefer, unless malaria is exceptionally intense, to treat infections as they occur rather than to take 7 grains of quinine a day for long periods of time. If they take this amount they will probably not suffer severely from malaria, since they will cure each attack almost as soon as it occurs, but there is usually a penalty attached. Slight attacks will come at irregular intervals which will be quickly suppressed; there will be days of indisposition and poor general health, greatly aggravated if the individual is one of the susceptible group. Much depends, of course, on the frequency of infection and the type of parasite. The patient may eventually become a chronic case of malaria without having had a sharp attack, or after long exposure over a period of years may suffer from severe attacks in spite of regular doses of quinine. Many of those who do not have this experience while taking prophylactic quinine have probably not been infected. The yellow-fever laboratory of the Rockefeller Foundation at Lagos was a continuous experiment in prophylactic quinine. Each 'tour' of service lasted eighteen months and was followed by a six-months' leave. Almost every one on the staff took from 5 to 10 grains a day when in Africa, and continued its use for a month or so when on leave. Those who took it with great regularity certainly

suffered less, during the first four or five years at least, than those who took it irregularly or not at all. Dr. Beeuwkes, the director, writes in an annual report: 'Our experience indicates that the prophylactic is of great value, for, though some of those who use it do not escape infection, the disease in infected persons is frequently retarded and symptoms do not manifest themselves at all or until the individuals return home and the drug is discontinued.' The degree of unavoidable exposure and the amount of transmission was such that the few who did not take quinine usually developed malaria promptly and had to be hospitalized, causing anxiety and the loss of valuable time. After several 'tours', some of those who took quinine most conscientiously began to have severe and repeated attacks of malaria.

Under less severe conditions the consensus of opinion among malariologists as to prophylactic quinine seems to differ, rather, from that of general clinicians, and to be less optimistic. For permanent inhabitants of a malarious zone prophylactic quinine can be of little service and may retard the development of immunity, while there is not the slightest proof that it will protect from blackwater fever. It should certainly be prescribed for prisoners, migratory agricultural labour, soldiers, or workmen who for a few weeks or months are obliged to complete a certain task in a malarious religion. Nevertheless, it may be unavailing in the case of certain parasites. The medical report of the Hamilton-Rice Seventh Expedition to the Amazon, by Strong, Shattuck, Bequeart, and Wheeler, states: 'It was in Vista Alegre on the Rio Branco that a number of the members of the expedition became infected with the disease [malaria] and that one, Dr. Koch, succumbed. The infection in this locality was obviously particularly severe, since the majority of the members of the expedition were taking prophylactic doses of quinine of 5 grains each day and 10 grains once a week.' It seems quite likely that the success of such treatment may vary with individual susceptibility to

malaria. The whole question is one on which the 'authorities' disagree.

However, even in its field of proven utility, quinine has always been a source of acute dissension. Those who used the drug with great success in northern Italy, India, or Spain were unable to understand the failures reported with the same methods in southern Italy, Panama, or the Balkans. The result was a tendency to lengthen the course of treatment, to increase the dose, and vary the intervals between doses in complicated ways, hoping to adjust the treatment to some supposed rhythm of parasitic insurgence and retreat. An enormous literature grew up based on differences of opinion, and its contradictory nature arose not from errors of observation, but from the protean nature of the human and parasitic elements involved. When Acton said that British and native soldiers in India were much more easily cured of *falciparum* than of *vivax* infections, there was immediate dissension in Italy. But now strains of widely diverse origins can be brought together and inoculated into patients lying side by side in the same hospital. When Indian and Italian strains of *falciparum* were both brought to London, it turned out that it required eight times as much quinine to control primary infections of the Italian as of the Indian strain. And as for *vivax*, a strain from Madagascar which was received in Amsterdam required different treatment and relapsed more frequently than a local strain obtained in Holland. Uniform results never can be obtained with quinine, because in each region malaria has a character of its own conferred upon it by the peculiarities of the local parasites. No doubt there are a multitude of strains of each species of plasmodium, differing as widely in virulence, response to treatment, and tendency to relapse as though they were separate species. Not only, however, does the character of malaria vary from region to region, but, considering the opportunities for mixed infections of an unknown number of strains, it

would be remarkable if any case of malaria resembled another. Thus the trouble with quinine was not, as people thought, in the way it was given without any rule or principle, so much as in the extraordinary diversity of the cases to which it was applied.

It was anticipated that in the malaria treatment of general paralytics it would be possible to get really uniform results with a chemically pure drug used on a stock strain of parasites of standardized virulence under controlled environmental conditions. No such uniformity resulted. Two cases hardly ever responded to treatment in exactly the same way, and the diversity was often astonishing. It was clear that some highly important variable was still evading our control. The nature of this factor had begun to make itself apparent from the very beginning of malaria therapy. James found rather extraordinary individual differences in his patients. In their reaction to malaria infection they seemed to fall by nature into three groups: the very refractory, the normally receptive, and the unusually susceptible. This was revealed not only in their degree of infectivity and in the nature of their attack, it modified in an important way the effectiveness of treatment. It seemed that a successful cure did not entirely depend on the germicidal potency of the drug employed, or even on the tractability of the parasite, influential as these factors are, but also to a large degree upon the co-operation of the patient himself. The patient had perhaps been considered too much in the light of a passive container into which drugs must be poured in large quantities in the hope of killing all the parasites at one stroke. Opinion now veered to the other extreme and questioned whether the drug had any direct action on the parasites at all. De Langen[1] and others held it more probable that quinine exerted its effect upon certain tissues and organs of the host, stimulating them in some way to resist and overcome the infection.

[1] *Trans. Far East Assoc. Trop. Med. 9th Cong.* **2**: 233, 1934.

This point of view was encouraged by some experiments which Mühlens and Kirschbaum[1] did with living plasmodia and quinine in a test-tube. Fresh blood full of parasites from a malaria case was mixed with equal parts of a 1 : 5,000 solution of quinine and left for twelve hours in the incubator at body-temperature. Now this is a concentration of quinine considered to be greater than any which can occur in the blood-stream, and yet the mixture of drug and parasites caused an attack of malaria when injected into another patient. When the strength of the solution was doubled, infection was still possible after five hours. The parasites had not been destroyed by the quinine.

This fact was soon confirmed by Yorke,[2] who then conceived the idea that quinine activates the immune mechanism of the body and that this in turn accomplishes the cure. The amount of quinine used would thus be relatively unimportant, since the result would hinge on the defensive powers of the patient. With Macfie he phrased the following hypothesis, often quoted:

'Quinine given to a patient whose blood contains numerous malaria parasites invariably destroys directly, or more probably indirectly, large numbers but not all of the parasites, thus setting free a considerable quantity of soluble antigen. The antigen prompts by stimulation of the host's tissues the formation of the immune body. The immune body, if present in sufficient amount, destroys the remaining parasites, thus resulting in sterilization of the infection and in the cure of the patient.'

This statement was successful in arousing world-wide discussion, for it provided a rational basis for a fact of common observation: namely, the influence of the personal factor upon the therapeutic action of anti-malarial drugs. It aroused powerful opposition as well, for there are serious difficulties in the way of accepting Yorke's explanation. In the first place, the role assigned to quinine hardly seems

[1] *Arch. f. Schiffs- u. Trop.-Hyg.* **28** (3): 131, Mar. 1924.
[2] *Trans. Roy. Soc. Trop. Med. & Hyg.* **18** (1–2): 13, May 1924.

necessary in view of the great natural destruction of parasites which, as we now know, goes on in the blood during the incubation period. It may be, of course, that plasmodia killed by quinine provide a more effective stimulant for the production of immune bodies than those engulfed by macrophages. Even so, the theory can hardly account for the interruption of an acute attack by quinine, because there is no time for the manufacture of specific antibodies. Prophylactic quinine taken over a period of weeks or months must destroy enormous numbers of young plasmodia, since its effect, as we know, is not to prevent infection but is always curative, aborting repeated incipient attacks. All this liberation of antigen does not prevent a sharp attack at last when quinine is discontinued. Lourie[1] has also pointed out that the eventual effect of a large dose of quinine on the blood picture in bird malaria is quite different from that of the so-called *crisis*, which is a phenomenon of immunity. Quinine in birds and in men interferes immediately with the normal growth and reproduction of the parasites, whereas immunity has little influence on such functions. And finally, Mühlens's experiment is not completely convincing. After all, it merely showed that all the parasites were not killed in the time allowed. It certainly did not prove that quinine has no direct action on plasmodia.

Thus, while almost everybody accepted the idea emphasized by Yorke that the capacity of the patient to develop and retain the immune body is of first importance to his recovery and freedom from relapse, no one was very clear about the role played by quinine in the process. In induced malaria quinine may be said to be completely ineffective at the moment of infection and in fact throughout the incubation period, but the amount needed to control acute symptoms becomes smaller and smaller as the attack progresses, until, after ten or twelve bouts of fever, as little as two or three grains (10–15 centigrammes) may suffice to stop all

[1] *Ann. Trop. Med. & Paras.* **28** (3): 255, Oct. 1934.

clinical signs for the time being. This seemed to indicate that while the prompt success of treatment is heavily dependent on the defensive powers of the body, the process of immunization need not rely very much, if at all, on treatment. In fact the suspicion grew that the taking of quinine, begun too soon or unduly prolonged, might, instead of stimulating the immune mechanism, actually slow it down or even put it out of commission. If we were allowed to choose the most favourable moment to begin treatment, consulting perhaps the patient's best interests rather than his comfort, might it not be in the middle of his attack rather than at the beginning of the febrile stage? Something over 200 years ago Dr. Thomas Sydenham had said, 'You must take care not to give the Jesuits' Powder too soon, before the disease has a little wasted itself, unless the weakness of the patient requires it should be given sooner.'

By this time the proper treatment of a case of malaria had come to seem, to the laboratory man at least, no simple matter. There was the patient, whose native resistance should be allowed to build itself up under the stimulus of an infection not too abruptly checked; there was, on the other hand, the parasite, with its strains of varying virulence and obstinacy which must not get out of control. Before undertaking to prescribe treatment, the conscientious physician, like a good general, would want to know as much as possible about the strength and disposition of the enemy, and about the terrain on which he must organize his defences. He would try to determine not only what species but what strain of plasmodium he had to deal with, its clinical virulence and response to treatment. It would be very important for him to know the degree of native or acquired immunity possessed by the patient, the stage of the disease, and any environmental factors which might influence recovery.

This was certainly a courageous approach to that refinement of medical technique which the old Professors of

Pharmacology used to refer to as 'elegant therapy'. It was a counsel of perfection which brought therapeutic research into inevitable discord with field practice. The lines were squarely drawn between all so-called 'standard treatments' for malaria and the new scientific kind of treatment adapted to the individual case. The old Procrustean style of general standard treatment recommended to everybody everywhere, and given with the idea of destroying the infection root and branch in a high percentage of the population, is an anachronism which has, I think, already been abandoned. It is futile, as we now know, to expect the same scheme of treatment to work equally well in different parts of the world. But some scheme of treatment is a practical necessity in every malarious place for the guidance of physicians and the simplification of dispensary work. As Sinton[1] suggests, the logical application of the new knowledge of malaria should be the formulation of '*local* standard treatments' suitable to different areas or countries, and designed to give the greatest benefit to the greatest number of persons for the money available. It is out of the question under ordinary conditions to formulate special treatments for individual patients. It would hardly be economical or administratively feasible even to adapt treatment to the species of plasmodium, not to speak of the different strains. What has been done is to take into account the ability of most infected individuals to build their own defences under the stimulus of a rational therapy. This can be accomplished in more than one way.

The proposal cautiously advanced in the Malaria Commission's report to delay treatment until the patient has been able to develop tolerance by having a certain number of paroxysms has had a very cold reception. The report may refer only to hospitalized cases, but even so no one would advocate withholding quinine for a moment in the presence of *P. falciparum*. But the difficulty is to make sure

[1] *Quart. Bull. Hlth. Org. L.o.N.* **4** (4): 643, Dec. 1935.

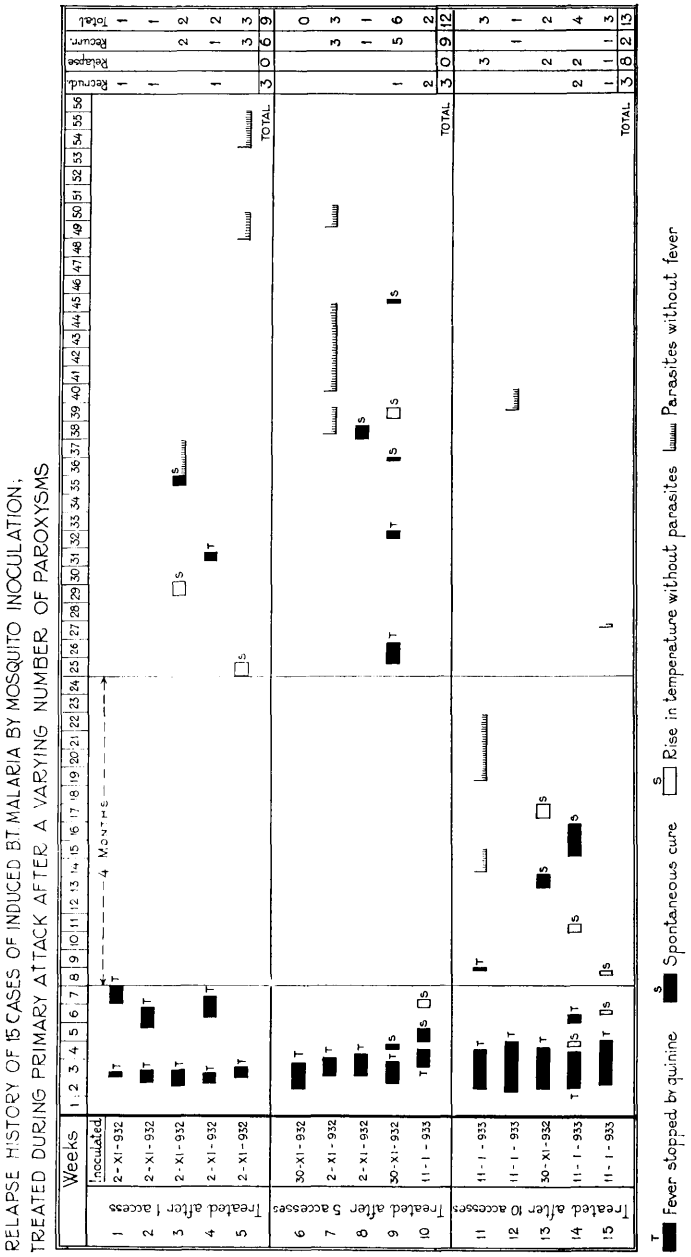


FIG. 19.

of its absence. In view of the fact that young ring forms are not always easy to classify, that mixed infections are not rare in which only one form is seen, and that fever is often a sufficient indication for treatment before parasites can be found, it is dangerous to delay therapeutic measures in any malaria case in a region where the pernicious form is possible. It has been suggested that in relapse, at least, there would be little danger in delaying treatment. Unfortunately in people exposed to malaria we have no way of distinguishing relapses from reinfections. Still, there are large European populations which have only *vivax* malaria and in which delayed treatment would not endanger life. Even so, it might not confer any real advantage on the patient. Fig. 19 shows fifteen cases of general paralysis in our series which were treated in three groups. The first group was allowed to have only one paroxysm, the second group five, and the third ten, before the attack was stopped with quinine. There were significant differences in the history of the three groups during the succeeding year. The first two groups had all their early recrudescences in the eight weeks following inoculation and after that were completely free from attack for almost four months. Then began a long period of frequent mild recurrences covering the rest of the year. In sharp contrast to this, the third group after the primary attack continued with one exception to have short bouts of fever, some of which required treatment, for another four or five months, upon which they were virtually done with the clinical reminders of their infection. It will be noted, however, that the freedom of the third group from relapse after the twenty-fourth week was gained at great expense of discomfort, fever, and doubtless of anaemia. This result could only be obtained by allowing ten paroxysms; five were not enough. Those suffered least who received prompt treatment, even though they had a considerable number of recurrences, all so mild as to terminate spontaneously within three or four days. Corradetti reminds

us[1] that the question of delayed treatment was considered and similarly resolved years ago by Grassi in his Second Report on Fiumicino in 1920. 'My experience leads me to believe', he wrote, 'that *in general* the cases of malaria which relapse the most at longer or shorter intervals are among those which at the first attack and in their recurrences are thoroughly treated by a prolonged administration of quinine. . . . I have thought that a repetition of febrile paroxysms without intervention of quinine provokes in the organism a reaction [attempt at immunization] against the parasites. . . . I would not, however, on this account allow the attack to go on without treatment because, after all, a relapse at the distance of a month or more . . . damages the organism much less than a series of paroxysms in rapid succession.' The chart also calls attention to the fact that many cures have been reported after an insufficient period of observation. Until the twenty-fourth week, if we exclude the immediate recrudescences which may be considered almost a part of the primary attack, only 20 per cent. of the fifteen cases had relapsed, but by the fifty-sixth week there had been some form of clinical manifestation in 53 per cent. of the group. Only one case (No. 6) on weekly examination showed no clinical or parasitic manifestations whatever after the termination of the primary attack.

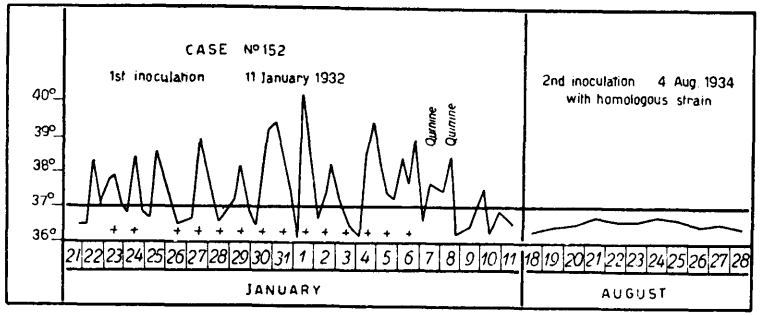
Delayed treatment obviously would not do and was also rather meaningless in a dispensary full of chronic cases. But the Malaria Commission's report had something to say also about cutting down the length of treatment. It was considered that the taking of quinine over long periods while the infection is latent is not merely useless, it may be retarding the development of those defensive powers, without which treatment seems to be unable to eradicate the parasite. This pronouncement was decidedly welcome even if it came a little late. Its effect was not so much to introduce a radical innovation in treatment as to confirm a

[1] *Riv. Malariol.* **15**, sec. 1 (3): 161, May–June 1936.

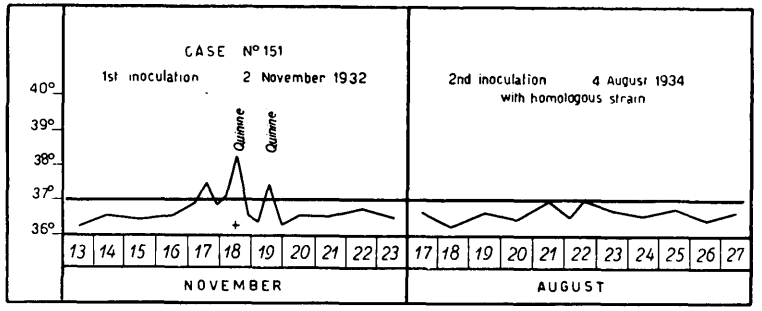
method already tentatively adopted in many places, partly for economy, partly as a concession to a rebellious public, and partly because it seemed to work rather well in practice. If science now declared the short treatment to be for the best interests of the patient, something of a weight was removed from the malariological conscience.

Science has not spoken yet with undisputed clarity in the matter. There are strong points against prolonged treatment, in particular the inability of infected persons to remain well and to stave off an eventual attack under a continuous régime of prophylactic quinine. Much of the evidence, however, is negative, e.g. that the suspension of treatment for certain periods does not lessen the patient's chances of recovery. On the other hand, Lourie has recently reported that canaries in which the characteristic acute stage of infection with *P. cathemerium* was entirely aborted by quinine treatment had subsequently as strong an immunity to superinfection as birds in which the primary infection was allowed to pursue an uninterrupted course. Thus a high degree of immunity may be built up during the actual course of rigorous quinine treatment. We have investigated this in a small way in our own laboratory with respect to human infections. A few years ago we treated a number of paralytic patients with the Madagascar strain of *P. vivax*, and some were allowed to have ten or more paroxysms during the primary attack, while others received prompt treatment and had a minimum of fever. We reinoculated them, by mosquitoes, two years later, and their resistance to superinfection, very high in all cases, showed no reduction in the individuals whose original infection had been controlled by quinine (Fig. 20).

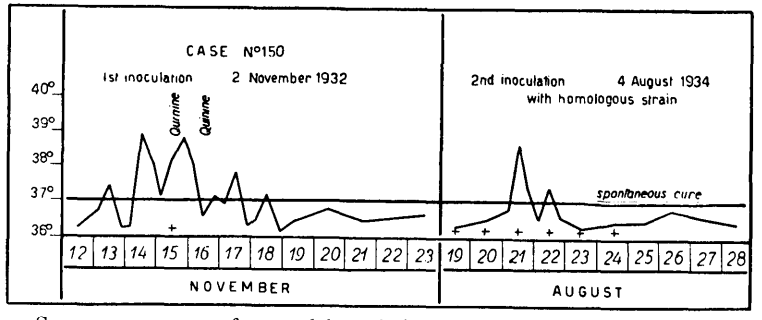
The fact is that the tendency of cases to relapse (and this is the only indication we have in nature of the effectiveness of acquired immunity in a malarious person) does not seem to be influenced a great deal one way or the other by quinine. We were impressed by the high general relapse rate of 50 to



Complete tolerance after long primary attack.



Complete tolerance after suppression of primary attack with quinine.



Spontaneous cure of second inoculation after treated primary attack. (*After* Mosna, 1935.)

FIG. 20. RESULT OF SUPERINFECTIONS WITH THE SAME STRAIN OF *P. VIVAX*.
On the days marked +, parasites were found in the blood.

70 per cent. after the long treatments of yesterday, yet Boyd reported that 60 per cent. of the paralytic patients in his laboratory in Florida relapsed when the primary attack was allowed to go on until it stopped spontaneously without any treatment whatever. Of these relapsing cases still untreated 60 per cent. relapsed again. It is difficult, therefore, to accept either the old theory that cases relapse because they are insufficiently treated, or the new one that they relapse from overtreatment. They seem to relapse for reasons independent of treatment. This, it seems to me, is the main reason why courses of treatment have been gradually reduced during the last ten years, until nowadays clinicians are often willing to suspend medication as soon as the infection returns to latency.

In 1925 the standard treatment in vogue almost everywhere was 60 centigrammes (10 grains) of quinine daily for eight weeks. At that time the Malaria Experiment Station in Rome was starting a larva-control experiment at Portotorres (Sardinia), coupled with a treatment campaign. Encouraged by Yorke's theory of the trigger action of quinine which appeared in 1924, the standard treatment in half the cases was cut to 1 gramme a day for six or seven days, which was more than sufficient to stop the acute attack. If fever returned, the same treatment was repeated. These subsequent attacks were all counted as relapses, since new infections had been reduced to a minimum by antilarval measures. In two years' observation of three hundred non-hospitalized cases it was found that the observed relapse rate after the long treatment was 40 per cent. and after the short treatment 46 per cent., a difference so small as to be negligible. It certainly did not compensate for the extra labour and expense involved in bullying apathetic villagers into swallowing quinine daily for two months.

The so-called 'Yorke treatment' within the next few years spread widely in Sardinia, and this was natural, because for once the easiest way seemed to have found some scientific

backing. It removed one of the greatest stigmas from the dispensary method, which was that the patient rather than the doctor determined the length of his own treatment. The universal failure of quinine to dry up the sources of infection was commonly laid to the indifference of the malaria victims themselves, who, as every one knows, are inclined to abandon treatment as soon as the acute symptoms subside. It now turned out that this might be sound practice after all. Quite independently of one another the various malaria stations of southern Europe created by the Rockefeller Foundation have all adopted the short treatment in slightly different forms. In Bulgaria Collins[1] has introduced what is probably the shortest treatment of all (four days), yet he reports that while there are more recrudescences immediately following the short treatment than the long—48 per cent. as compared with 30 per cent.—the former over an extended period affords greater freedom from attack. In Spain Hill[2] was able to follow forty-eight cases carefully for a year after the short treatment, and of these 55 per cent. relapsed, which is the expected number after any form of quinine treatment, but half the relapses occurred between fifteen and thirty days after recovery from the primary attack. In Greece Balfour[3] experimented with five-day, ten-day, and fifteen-day courses. Fewest relapses (45 per cent.) were observed after the ten-day course. So far as I know, no one has shown under European conditions that the effectiveness of quinine in dispensary treatments can be increased by giving it for more than ten days at a time, or in larger doses than 1 gramme a day. We have given up at last trying to eradicate infections in one step with our present therapeutic agents, and we are frankly satisfied with preventing mortality and maintaining malarious populations in a condition to work. The infrequence of late relapses

[1] *Am. Jl. Trop. Med.* **14** (4): 329, July 1934.
[2] *Jl. Am. Med. Assoc.* **104** (26): 2329, 29 June 1935.
[3] *Riv. Malariol.* **15**, sec. 1 (2): 114, Mar.–Apr. 1936.

following a minimum of treatment suggests that in this way we are in fact hastening the establishment of an equilibrium between host and parasite, which may lead to eventual cure without undue molestation from acute attacks.

Empirical as all this evidence is, there now seems to be no one to defend those protracted courses of quinine or the 4-gramme doses advocated only yesterday by high authority and buttressed by an impressive array of well-attested accomplishment. The classic eight weeks' treatment, after centuries of faithful service, has suddenly been abandoned by the roadside without complaint or ceremony. The Malaria Commission of the League of Nations has now delivered the *coup de grâce* by recommending in substance (1933) that treatment be continued in all types of malaria not longer than a week, if by that time symptoms have subsided completely, but that (especially in *falciparum* infections) close watch be kept for relapses, which should be treated in the same way.

That the new fashion in treatment would have made its way eventually into the most conservative circles, through the irresistible pressure of field experience backed up by laboratory evidence, is not to be questioned. One of the notable accomplishments of malaria therapy has been to put the use of quinine at once on a more rational basis. We have to admit, however, that this has been greatly accelerated by the appearance of some competitors on the horizon. The new synthetic drugs have at one stroke destroyed the secular monopoly of quinine and put it squarely on the defensive, both in the market-place and in the clinic. We were solemnly informed some years ago that the price of quinine had reached an absolute minimum, and that any further reduction would drive the planters to destroy the cinchona trees and replace them with tea. Nevertheless, the price has come down. At the same time there has been a healthy deflation in estimates of its medicinal virtues. Quinine has been forced by the enemy out of a score of

untenable positions into a stronghold which it is prepared to defend.

These new drugs are an outcome of an intensive search for quinine substitutes by German chemists after the World War.[1] At first time was wasted in trying to synthesize quinine, but soon entirely new compounds by the thousand were being prepared by the organic chemists. The difficulty was that while we can predict almost everything about a new substance whose formula we know—weight, solubility, reaction, and even colour—we cannot foretell its pharmacological and germicidal action. This must be discovered empirically by trying it out on a large number of infected individuals. But to come to any clear idea of the efficacy of a drug under natural conditions is time-consuming and difficult in the extreme, as we have just seen in the case of quinine. It was probably a disconcerting thought to the early experimenters with synthetic drugs that, in three hundred years of continuous trial, no general conclusions were ever reached with regard to quinine which were not immediately contested in the most authoritative way. It was certainly out of the question to make field tests on thousands of new preparations.

Roehl, a German medical research worker, brought order into chaos by inventing a 'claustrated' experiment, an advance in methodology long overdue. The test-tube was a canary infected with a given dose of a known variety of bird malaria. The drug to be tested, in measured quantity proportioned to the weight of the bird, was introduced by stomach tube. If the drug had a certain established minimum influence on the infection in the bird, it was considered worth trying on laboratory animals to establish its general toxicity, and on man to test its effect on the plasmodia of human malaria. Human cases in European hospitals were not lacking, but they were not perfectly suitable to the purpose. Hospitals for tropical diseases harboured only malaria cases relapsing from infections of unknown origin and nature, while the induced malaria of general paralytics was being inoculated at that time by blood-transfers from one patient to the next. Such an infection was much more responsive to treatment and less liable to relapse than natural malaria. Yorke and Macfie, of the Liverpool School of Tropical Medicine, were the first to begin to infect general paralytics by means of mosquitoes (August 1923), and this is an important milestone in malariology. James soon developed a technique for the transmission, treatment, and observation of laboratory malaria, at Horton Mental Hospital, which has served as a model for such experimentation everywhere. The effect of different drugs on a given strain of the malaria parasite could now be tested in human beings, and the effect of the same drug on different parasites.

Of all the chemical compounds which have run the gauntlet of the Roehl test and induced malaria to date, atebrin and plasmoquine alone stand out as possessing definitely new and valuable qualities. Atebrin was synthesized by Mietzsch and Mauss in 1930 and tested on birds by Kikuth. Plasmoquine was made synthetically by Schulemann, Schonhofer, and Wingler in 1925, tested on birds by Roehl, on guinea-pigs by Sioli, and on cases of malaria by Mühlens. In general architecture both bear a certain resemblance to quinine, in that they all consist of a benzol ring-system or nucleus connected by a special link to a basic component, the hydrocarbon side-chain. Atebrin, which chemically has no components in common with quinine, is considerably like it in effect. It possesses most of the virtues of quinine (with a distinctly more powerful attack on certain strains of *falciparum*) without its defects. Its advantages lie mainly in convenience of administration, absence of those annoying nervous effects of quinine called *cinchonism*, and in the five- to seven-day course of treatment, which seems to be followed by fewer relapses than a similar course

[1] Schulemann, W., *Trans. Roy. Soc. Trop. Med. & Hyg.* **26** (2): 120, 11 Aug. 1932.

of quinine. On the other hand, it may cause mental derangement, and, in children, collapse and convulsions in a small percentage of cases, so that, on the basis of the experience gained in the recent epidemic, the officers of the Ceylon Medical Department[1] thought it unsuitable for mass distribution. How unsettled the whole matter is may be judged from the fact that Komp and Clark[2] have arrived at precisely the opposite conclusions after three years' experience with the drug. 'In our hands', they write, 'atebrin has been much less successful than was hoped in preventing relapses, especially in young children, but we have observed no toxic effects nor any contra-indications to its use.' There is an interesting observation by Chopra and Das Gupta[3] which seems to show that the mode of action of atebrin and quinine may be quite different. Newly infected monkeys always relapse acutely after atebrin and each time so severely that they may die if not treated, but quinine tends to establish chronic cases in monkeys from the start, characterized by long latencies and mild recurrences. It may be that atebrin has a more direct destructive action on the parasite than quinine, evident, according to more than one observer, in the altered appearance of the parasite itself under atebrin treatment. The makers state that it is a vital stain with a special election for red blood-cells, which it can penetrate with ease. If taken long enough it ends by staining all the tissues of the body, turning skin and sclera yellow. This certainly explains its disposition to accumulate in the body, and possibly its action on the parasite as well. Its principal value lies in the peculiar properties which set it apart from quinine. For now we have two distinct and effective agents instead of one, to meet specific resistances of the parasites and idiosyncrasies of the host.

Plasmoquine stands chemically between quinine and

[1] Ceylon Govt.—Sessional Paper 22, Sept. 1935.
[2] *Am. Jl. Trop. Med.* **15** (2): 131, Mar. 1935.
[3] *Ind. Med. Gaz.* **68** (9): 493, Sept. 1933.

atebrin, having the quinoline nucleus of the former and the identical link and side-chain of the latter, but it is unlike either in its action. Even in minute quantities it sterilizes or destroys the sexual forms (gametocytes) of all malaria parasites and thus prevents the transmission of the infection to mosquitoes. This is its one certain accomplishment. Its value in treatment is still under warm discussion. Admittedly it has no effect on the sporozoites injected by an infected anopheline, and it is so toxic that it cannot be safely used in the dosage necessary to combat the trophozoites which produce the acute attack. Nevertheless, Sinton and Bird,[1] working with a tough lot of old recurring *vivax* cases in India, discovered that the combination of a little plasmoquine with the quinine reduced the percentage of relapse in the first eight weeks from sixty-five to less than ten. Later, Dixon[2] kept 600 cases in Indian soldiers under observation for ten months to three and a quarter years, and observed a relapse rate of less than 5 per cent. after the same mixed treatment. Now, of course, it has been shown over and over that neither quinine nor plasmoquine in ordinary doses can prevent relapses. For this reason the Malaria Commission has sought to discourage the use of plasmoquine as an adjuvant to quinine and atebrin during the acute phase of the disease, on the ground that, as the two drugs do not combine to form a new compound, each drug can only exert its own specific action, and the 'proposition that relapses can be reduced by giving ineffective doses of both drugs is paradoxical'. Thus are stubborn facts as nothing to a stubborn theory!

But the controversy is really not so much over facts as over procedure. The Commission, absorbed in the scientific side of the problem, with a powerful instrument of research at hand, are loath to see these new drugs, while still in the experiment stage, being tried out in arbitrary

[1] *Ind. Jl. Med. Res.* **26** (1): 159, July 1928.
[2] *Jl. Roy. Army Med. Corps*, **60** (6): 431, June 1933.

ways without laboratory sanction. Remembering the unhappy history of quinine therapy, they are naturally afraid the bungling clinicians will only 'bring further confusion into a problem which is already immensely complex'. The clinicians, on the other hand, having found out by trial and error that under local conditions a certain drug or combination of drugs seems to work in practice, are not disposed to mark time until the laboratory discovers how this is possible. And finally the health officer, interested in medical assistance not as an end but as a means to reduce malaria transmission, finds the laboratory method inadequate as yet to resolve the particular points which give him the most trouble. For there are three important elements in his problem which are excluded from hospitals for general paralytics: children, reinfections, and unfavourable conditions of life.

The relapse rate will differ according to the number of children in the group under treatment. 'Every one knows', wrote Celli, 'how obstinately malaria relapses in children.' Kligler,[1] after an experiment with plasmoquine in Palestine, gives warning that it is the children under six who may wreck the hope of success in any attempt with drugs to control malaria. In one of our treatment centres, Posada in Sardinia, the malaria curve in children under twelve reached almost the same height in March 1930 as it had in July–August 1929. Almost all the younger children relapsed, in spite of a sixty-day course of quinine. Growing children, according to Kligler, acquire immunity less easily than adults from primary attacks, and the final estimate of relapse-preventing drugs must be based on tests of the younger age-groups.

Exposure to constant reinfection also changes the whole aspect of the problem. Drugs are required which can be used *instead of* anti-mosquito measures, and the bulk of the defence work will fall to the individual powers of resistance.

[1] *Trans. Roy. Soc. Trop. Med. & Hyg.* **27** (3): 269, 30 Nov. 1933.

This, unlike the passive resistance of a stone wall, will be the aggressive reaction of a population on a war footing. It can only be kept at a high level of efficiency by the constant stimulation of attack, and hence treatment should be used to further the development of immunity if this is feasible. This plan adopts the best features of nature's method of building a high general immunity by selective mortality over a long period, but seeks to avoid the slaughter of the innocent. Such, according to Sinton, are the considerations which in our present state of knowledge should guide the clinician and field worker as distinct from the research or laboratory worker. In populations of individuals in whom the chances of reinfection are comparatively slight, the treatment adopted should aim, he thinks, at a radical cure of the infection. But in my experience, if the freedom from infection is due to the suppression of mosquitoes, malaria melts away so rapidly that no special treatment is necessary. In the end a small group of susceptibles will haunt the dispensary, relapsing almost indefinitely, and constituting an excellent test of the powers of modern eradicative therapy.

Unfavourable conditions of life are stated in all the books to have the greatest influence on susceptibility to malaria, response to treatment, resistance, chronicity, and relapse. Such conditions include malnutrition, fatigue, climatic exposure, overcrowding, disease, and economic strain in all its forms. Professor Fermi,[1] on the basis of a straw vote taken by consulting the writings of a great many prominent malariologists, living and dead, has placed *benessere* or well-being at the top of the list of the causes of malaria regression in modern times. This is why malaria is generally classified as one of the social diseases. Unfortunately no attempt has ever been made to measure the effect of these detrimental factors, and so this still remains a matter of opinion. Until some one has tested the influence of economic strain on a group of infected monkeys, it can only be mentioned as a

[1] *Regioni Malariche: Vol. I—Sardegna* (Rome, 1934), p. 876.

factor of unknown importance differentiating laboratory cases from people in malarious villages.

Whether, in the face of all these natural obstacles, and of the notorious indifference of malarious populations, the health officer has a weapon in these new drugs and new methods of treatment which he can effectively and economically employ in malaria control, has not been shown. Between laboratory results and field practice must come a great body of experimental work under natural conditions which has hardly been begun. Perhaps it is not too much to hope that the chemists will give us some time a drug powerful enough to iron out all the variables and to cure all types of infection in almost any individual.

FIG. 21. BURSTING OF A RIPE OOCYST ON THE STOMACH WALL OF AN INFECTED ANOPHELINE MOSQUITO, LIBERATING SPOROZOITES INTO THE BODY CAVITY, DESTINED TO FIND THEIR WAY INTO THE SALIVARY GLANDS OF THE INSECT

(*From the* Inst. of Pub. Health, Rome)

VIII

THE PECULIARITIES OF TEMPERATE CLIMATE MALARIA

The first figs and the heat bring out the undertaker with his black attendants. Every father and fond mother turns pale with fear for the children, while diligence in the Forum's petty business brings on fevers and unseals wills.

HORACE, *Ep.* I. vii.

THE amoeba of malaria is certainly an unusually enterprising bit of protoplasm. Coming from an undistinguished family at the foot of the zoological scale, it has worked its way into a position of influence in two separate organic spheres, human and insect, exploiting both to such advantage that it has become Enemy No. 1 of mankind. I do not know where else the adaptive power of protoplasm is so well illustrated. The parasite of malaria accommodates itself to quite dissimilar biological environments, passing easily back and forth from one temperature to another. Being a foreign body of an aggressively noxious kind, it has to resist powerful natural forces doing their best to dislodge it. It not only resists, but it accomplishes the feat of multiplying in both hostile situations.

To do all this the plasmodium has evolved a number of physical transformations, from ring-form to sausage-like gametocyte and slender double-pointed sporozoite. These metamorphoses serve various ends: the invasion of a new host, the escape into latency from an untenable position, the need of sexual dimorphism for the reproduction of its kind. It happens that, whenever it turns into anything but a simple growing amoeba, it puts itself beyond the reach of quinine and the other drugs like it.

The differentiation into three or four species and an unknown number of strains is doubtless a scheme for expansion and colonization—another adaptation enabling a

tropical form to increase its range and to invade new territories with unfamiliar climates and strange vectors. *Vivax* can infect mosquitoes at a lower temperature than *falciparum*, and de Buck has found that his Holland strain of *vivax* will develop and produce sporozoites in the mosquitoes at a temperature which paralyses the Madagascar strain. It is thus fitted to survive in northern Europe. But to do this the curve of its gametocyte production must also coincide with the biting season of the northern anophelines. The happy adjustment of parasite to vector in any area has come about through a weeding-out process, in which ill-adapted strains (and species) have failed to be transferred at proper intervals and have consequently become extinct. Thus it is theoretically possible to have at the same time dangerous vectors and very little transmission. Knowles and Basu[1] explain the low endemicity of malaria in Calcutta as compared with Bombay, in spite of the presence of the same carrier species *A. stephensi*, by the lack of correlation between the mosquito breeding season and the gametocyte season of any of the parasite species. The peak of *stephensi* production comes in July, but that of *falciparum* incidence falls in October, of *vivax* in April, and of *malariae* in January.

The principal obstacle to the invasion of Europe by the malaria organism was not, however, the question of adjustment to a new mosquito; it was winter—an annual intermission in nature affecting all living things, and among them the mosquito and the plasmodium. Both of them had to find a way of surviving the winter. Yellow fever, for instance, is unable to do this. The virus requires such frequent transplanting in man that the chain is broken when the mosquitoes disappear in the cold weather, leaving only their eggs to bridge the gap between one summer and the next. The infection always has to be reintroduced into temperate climates each year from the tropics.

[1] *Rec. Mal. Surv. Ind.* **4** (3): 291, Sept. 1934.

The anopheline survives the winter by an invention of nature called 'gonotrophic dissociation'. In response to a stimulus which no one has ever been able to discover, the reproductive functions of all *maculipennis* mosquitoes are switched off before the end of summer, while the mosquito is still actively biting. The blood meals, instead of ripening eggs as before, now go to build up fat to carry the insect over the winter. Most of the races hibernate completely, frozen up in protective isolation, enabled by a greatly lowered rate of metabolism to live entirely on their stored-up fat. One race (*atroparvus*) prefers to remain in more comfortable quarters in warm, occupied houses or stables, biting from time to time to replenish its rapidly failing stores, but keeping its ovaries in some mysterious way inactive until a given moment in spring. In the range of this mosquito we get those focalized winter-time infections of malaria in northern Europe, which through a natural grouping of cases by families gave rise to the 'malarious houses' of England and Holland.

The winter pause in reproduction is something more, however, than simple hibernation. In the south of Europe, where the winter may be very short indeed, the period of suspended ovarian activity may actually run its whole course and be finished before winter has fairly begun. In Albania we have often found females of the upland and so-called hibernating races in the stables full of blood and eggs in February, faced with a long stretch of snowy weather before they can possibly establish the first spring generation. The same thing has been noticed about non-hibernating *atroparvus* in Spain by de Buen, who believes that they actually lay their eggs on the inhospitable waters but that the larvae do not survive. Evidently the sterile period is one thing and hibernation is another, and they are not always well co-ordinated in southern latitudes, especially at a certain elevation. It suggests that length of day or some other seasonal phenomenon besides temperature gives the annual

curtain-signal bringing to an end the season of reproduction. In the laboratory, colonies of *atroparvus* can be maintained indoors the year round under quite artificial conditions of light and temperature. Winter means nothing to these captives in their carefully regulated climate, yet in the late autumn they also begin to be refractory about laying eggs at the same time as their fellows out of doors, and the colony is only tided over a relatively sterile period of a month or two by a few apparently exceptional individuals in whom ovarian inertia can be overcome by forced feeding and individual solicitation. Even so the eggs obtained are occasionally infertile. Roubaud[1] calls it an 'annual cyclic fatigue phenomenon' unconnected with cold, something like that, I suppose, which occurs in hens. If so it is strange that it has not been reported in the tropics, but we are singularly weak on anopheline physiology. At any rate it seems more than accident that it coincides more or less closely with the winter season in Europe, permitting the northern anophelines to prepare themselves for the cold weather. Possibly only those few species in which it does so coincide have been able to maintain themselves in the temperate zone. The differences between races in mode of hibernation, exhibited mainly in choice of refuge, would then be superficial, developed on the basis of a common physiological necessity.

Not many anopheline species are able to hibernate, and so withstand the intemperances of temperate climates—only seven in Europe and eight in America, as compared with thirty-five or forty each for Africa, Asia, and the American tropics. It is much the same with the flora of these regions, which in the tropics consists of an enormous variety of mingled forms, mostly annuals and shrubs, belonging to species which are represented in the north by a few large trees in great stands; and this for the same reason, the necessity of surviving the long winter. But that there are

[1] *Riv. Malariol.* **10** (1): 1, Jan.–Feb. 1931.

so few temperate climate anophelines has unfortunately made no difference to the spread of malaria. Of the 150 anopheline species there are only a dozen notable vectors in the world, and in any one region, whether tropical or temperate, there are not apt to be more than two dangerous mosquitoes. The island of Ceylon alone has eighteen species of anophelines of which only one is known to be a carrier. Europe therefore has more than its share with three or four. What is of importance is that the anopheline survivors of the winter are relatively few and the season of activity is very short—one or two generations throughout the whole summer at the most. In England or in the Black Forest, for instance, the female issuing from hibernation in the spring may be separated by only one generation from the female which in early August begins to lay up fat for the next winter. This may perhaps be compensated by a longer life and fewer enemies, but we really know very little about the natural history of the anopheline mosquito. In southern Europe malaria often uses a combination of two or more anopheline species to prolong the season. In the Balkans *elutus* follows *maculipennis* and *superpictus* follows *elutus*, and though none of them has a very long season the combined transmission period often lasts from May to October, with a correspondingly intense malaria.

The European anopheline, on the other hand, has certain advantages. The tropical health officer or malariologist on periodic visits to the north is always astounded anew at the great size and prodigious numbers of our European anophelines. The difference in numbers may be more apparent than real. It happens that *maculipennis* spends most of its life within doors, and so we see tens of thousands in stables. Malaria vectors in the tropics may be as numerous, but they do not often remain indoors after they have fed, and what becomes of them in the day-time no one knows. It is, however, the flight range of the European anopheline which is particularly impressive. Perhaps the long northern twilight

gives it scope for greater activity. In the tropics in general, if all the breeding-places are destroyed within a radius of half a mile, few anophelines will reach the centre, but by hard experience those who have had to do with malaria control in Europe know that antilarval measures must be carried out to 4 or 5 kilometres to be successful. This means that sufficient numbers can fly 2 to 3 miles to maintain endemic malaria. We do not know the reason for this great and important difference. *Maculipennis* is, of course, an enormous insect by tropical standards, and yet the tiny *superpictus*, whose range only just touches Europe from the south, has an almost equal flight capacity. We have thought that it reached one of our Calabrian towns from a distance of 4 miles, and Wenyon, speaking of a hospital station in Macedonia during the War, says that thousands of *superpictus* were caught in hospital marquees protected often by a mile of antilarval work. *Elutus*, the most dangerous of them all, is a strong flyer. Kligler has described its long pre-hibernation migrations in Palestine, in which large groups may cover as much as 8 miles, and Herms has followed the Californian *maculipennis* even farther in its dispersal flights.

However, we have never been quite sure how far *maculipennis* habitually flies merely for food in the summer. This was cleared up recently by a unique experiment in Holland. The formation of a new great 'polder', the Wieringermeer, by diking off part of the Zuider Zee, enabled Swellengrebel[1] to make a crucial test. New polders do not breed anopheles for at least a year after they have been drained and hardly at all for three or four. During the first year the land is in the quagmire stage, like a hydraulic fill, with the water still too salt for anopheline breeding. Two pigsties were built at 3 and at 5 kilometres (2 and 3 miles) from the old land, and between 1 June and 15 September 1931 new anophelines were found in both of them each day. The average daily

[1] *Quart. Bull. Hlth. Org. L.o.N.* 3 (3): 441, Sept. 1934.

catch at 3 kilometres was thirteen females and two males, and at 5 kilometres seven females and one male. This shows that the males can fly far and do not necessarily remain in the vicinity of breeding-places. The wind aided these flights, for the insects were most numerous on days after a land breeze. The next year a new pigsty was built at 10 kilometres (6 miles), and now the anophelines in all three greatly increased, not because of any breeding on the polder, for this had not yet begun, but owing to the abandonment of larva control at the nearest point on the old land. The average daily catch was actually sixty-nine anopheles at 10 kilometres, and upon staining and releasing a great number on the old land a stained male and female were caught at 14 kilometres ($8\frac{1}{2}$ miles) upon the third day (Fig. 22).

We have then, as the malaria vector of Europe, a powerful insect of great size which has evolved a method of surviving the coldest winters from Scandinavia to Archangel; can in a short season build up a great population, and has an enormous flight range, securing for it wide possibilities of food and shelter and increasing man's difficulties in its control.

But the parasite is equally resourceful. Since its life-span is fixed and its migrations involuntary, it assures the continuity of its existence from year to year by a long and protected latency in the human body. *P. falciparum* is not so well suited to this necessity. It is adapted to the more constant environmental conditions of the tropics and to frequent and regular passages between mosquito and man. In the Mediterranean basin, with its short winters and high level of transmission maintained by such active biters as *elutus* and *labranchiae*, *falciparum* can flourish in hot, wet years, but even in this sub-tropical zone it falls to a low level in the dry years. It is an infection which tends to die out during the winter or whenever transmission fails, since it runs an almost acute course with frequent recrudescences

at first, but few widely spaced relapses. Some infections, however, always get through the longest winter by dint of

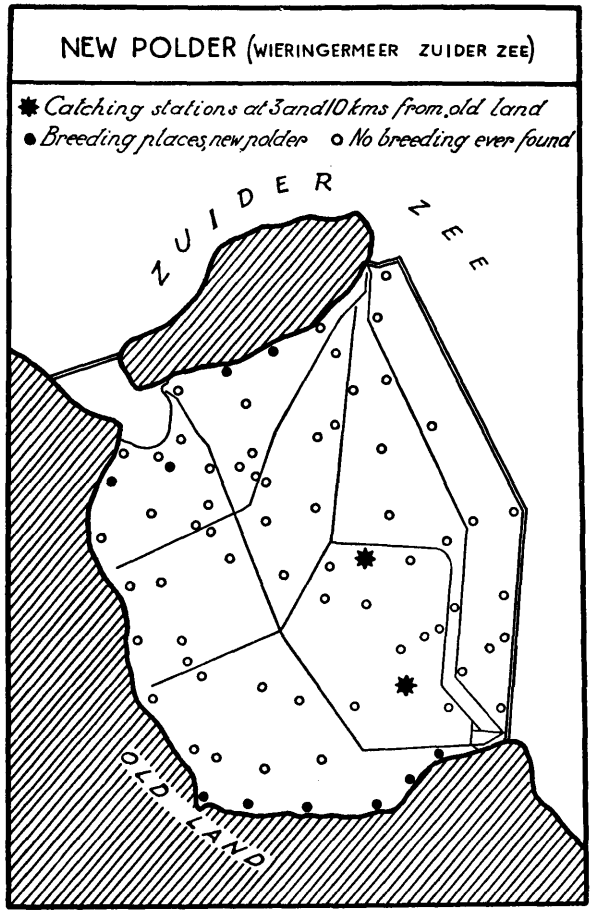


FIG. 22. FLIGHT RANGE OF *A. MACULIPENNIS* IN HOLLAND.

many recrudescences and a few obliging long-time carriers. One case on record remained a carrier continuously for 156 days. What it needs to leap the winter is a good running start with a late autumnal epidemic wave, hot weather, and a high inoculation rate. When *vivax* malaria is fading out

with the summer, *falciparum* infections are increasing, and the curves cross in August or September, as Wenyon found in Macedonia. It is for this reason that some of the late-season anophelines, like *superpictus*, are usually found carrying *falciparum* infections, but it is without doubt a seasonal coincidence and not a selective process. We cannot, however, discard off-hand the idea that some species of anophelines may be refractory and others perhaps unusually receptive to certain strains of parasites. James was not able to infect British *maculipennis* with Indian or African *falciparum*, whereas they were easily infected with the Italian strain.

Each spring in European latitudes is a critical period for *falciparum*. At the season when the anopheles begin to fly, the parasite can muster so few of the crescent forms which infect mosquitoes that to the earlier malariologists, such as Grassi, Dionisi, and Marchiafava, it remained an unsolved problem how the regular summer epidemic of *falciparum* malaria could be built up at all out of the rare spring gametocytes to be found in the latitude of Rome. 'In the course of the winter', wrote Bastianelli and Bignami,[1] 'relapses of the estivo-autumnal fevers become more and more infrequent until in spring it is almost impossible to find a patient with crescents: in fact, in all of Ostia, in spite of repeated examinations, we were not able to find a single one.' Dionisi examined all the labourers in Maccarese, also on the Tiber delta, without finding one gametocyte carrier in June; nevertheless the estivo-autumnal epidemic broke out quite suddenly, as usual, early in July.

The apparent lack of infective elements in the human population in spring has often raised the question of the possibility of the overwintering of *falciparum* and of the other species in the glands or stomachs of hibernating mosquitoes. Epidemiological evidence, however, is all against it. Babies born during the winter in Posada (a

[1] *Communic. X Cong. Soc. Ital. Med. Interna*, 26 Oct. 1899.

village in Sardinia) did not have malaria until June, although the mosquitoes came out of hibernation in March, and this seems a very delicate test, for *falciparum* has no prolonged initial latency. Balfour reports that in Greece, in a village with a 100 per cent. spleen rate, fourteen babies born after 1 November did not have malaria until the new generation of mosquitoes appeared the following year. When infected mosquitoes began to be preserved alive in laboratories for the purpose of inducing malaria in general paralytics, it was found that they lost their infectivity in 40 to 50 days, and upon dissection the oocysts and sporozoites showed signs of degeneration. And now Swellengrebel, in thousands of dissections of anopheles taken in houses in a malarious village in Holland, has found that in nature the degeneration of *vivax* oocysts and sporozoites begins at the end of October, involves three-quarters of the infected glands and two-thirds of the stomachs by 1 December, and virtually extinguishes mosquito infections by 31 December. Boyd has proved that this process proceeds even more rapidly in a tropical form like *falciparum*, and therefore human cases alone must bridge the gap between one malaria season and another.

It was never necessary to resort to over-wintering mosquito infections to explain the continuity of *falciparum*. There are two types of carrier which can be depended on to furnish all the gametocytes necessary: the babies and the occasional non-immunes of older age-groups. Schiassi[1] says that Grassi and Dionisi did not find crescents in the spring because they did not examine any babies, and besides, they did not use thick blood smears. Gametocytes occur in adults but they are not easy to find. In our routine thick-drop examinations in Posada, which was under observation for several years, we never found a crescent carrier over twelve years old before July (Fig. 23). It is not a question of age, but of the number of attacks a person has had. Crescents

[1] *La Malaria e le sue Forme Atipiche* (Bologna, 1923), p. 48.

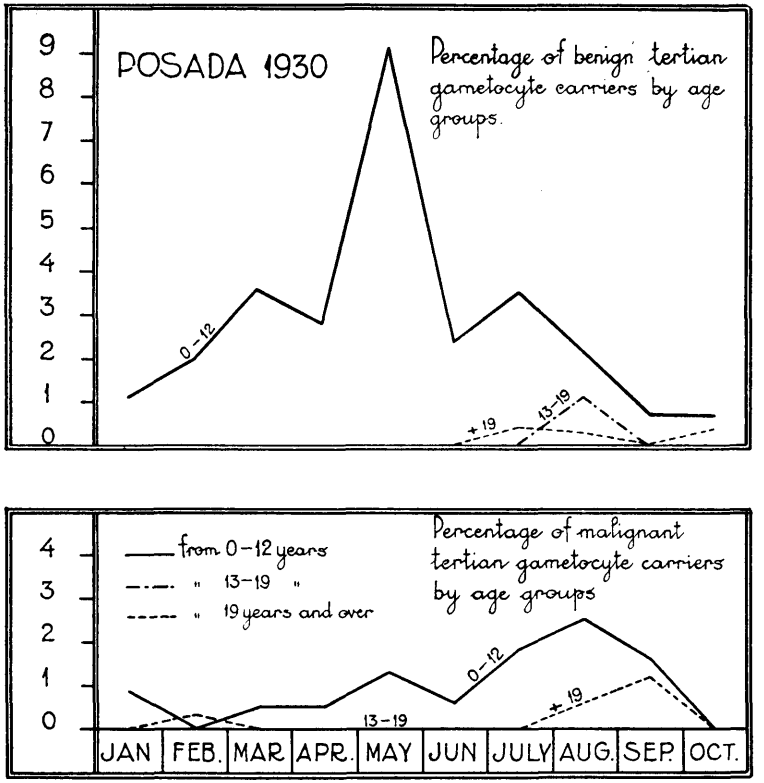


FIG. 23. CHILDREN AS GAMETOCYTE CARRIERS IN POSADA, SARDINIA.

Note the spring wave of *vivax* carriers above and the failure of the microscope to reveal either *vivax* or *falciparum* carriers in adults during the pre-epidemic season.

diminish with each relapse, as seen in the average numbers reported by the Malaria Commission of the League[1] from a series of cases in general paralytics:

Primary attack . . .	161	crescents in	100 fields
2nd relapse . . .	37	,,	,,
4th ,, . . .	21	,,	,,
6th ,, . . .	10	,,	,,
8th ,, . . .	1	,,	,,

[1] *Quart. Bull. Hlth. Org. L.o.N.* **2** (2): 181, June 1933.

The principal danger to the community does not come from the ordinary chronic case but from the occasional individual who, for one reason or another, is a heavy carrier, or who constantly relapses. Bastianelli and Bignami reported in 1899 that in the Santo Spirito Hospital of Rome, into which most of the severe cases of malaria were annually gathered from the Roman Campagna in autumn, there were that year only 'a very few patients between the 20th and 30th June—five with estivo-autumnal infections of which two were relapsing cases which had had fever at irregular intervals since October of the previous year, these last with *crescents in their blood*'. With these few elements to start with it takes a long time each year to build up a *falciparum* epidemic, but with the co-operation of two or three different species of anopheles to lengthen the season, it can just be done in the south. It always fails in the north and the infection dies out whenever it is introduced. *Falciparum* is naturally the first species to disappear in the sub-tropics under any kind of pressure, whether of climate or of man's preventive activities. Interruption of transmission, or even a significant reduction in the frequency of passage, puts it at a serious disadvantage.

Plasmodium vivax, on the other hand, is perfectly adapted to the northern winters, which it survives by lying latent in the human body for seven or eight months on end. This may be inherent periodicity independent of season and successful only because the mass of infections occurs in autumn, or the precession of the equinoxes may in some mysterious way control its alternating phases. At any rate, there is a great flood of *vivax* gametocytes in spring to greet the newly emerged anophelines, at the time *falciparum* is beginning the annual task of building up its numbers from a few scattered seeds. In the far north late summer infections may prolong their incubation periods to appear for the first time in the following year, and *atroparvus* assists by refusing to hibernate and biting throughout the winter.

But in each area the various strains of *vivax* all seem adapted to the local mosquito cycle, and it is probable that this is not purely fortuitous but that those strains which were not so adapted have died out.

Quartan is still an unsolved problem in epidemiology. It reaches its peak quite frequently in early winter, because of its relatively long incubation period, but its appearance in this off-season may be due to latency of *vivax* and the failure of *falciparum* at that time. It hangs on by its persistence in the body and the slow development of the immune reaction. Forced into obscurity by *vivax* and *falciparum*, it outlasts them both and finds its rare occasions for transmission sufficient to preserve the species.

Thus the anopheline and the parasite have overcome the difficulties of the northern winter in the same way. Both are hibernating organisms, and, in fact, in the far north the whole annual epidemic, finding it impossible to organize transmission on a large scale before the end of the year, hibernates until spring, when it can have the summer before it; but in the process it has to drop *falciparum* by the way. Figs. 24–7 show the characteristic modification of the annual curve of malaria as one proceeds northward from the tropics. Note the predominance of *falciparum* (M.T.) over *vivax* (B.T.) in Cuba (Fig. 24). *Vivax* is a month behind. In the sub-tropics (Fig. 25) *falciparum* still predominates but comes later in the year. It bursts forth abruptly in July. *Vivax* is now important, with a wave of relapses in March. Farther north (Fig. 26) the anopheline season becomes shorter and shorter; *falciparum* gradually diminishes, and the peak of *vivax* infections is deferred until it becomes the autumnal form of malaria. Finally in Holland (Fig. 27) *falciparum* can no longer bridge the gap from summer to summer and has disappeared. Even *vivax* finds the season of transmission inadequate. The spring peak of cases derived from infections of the year before now occupies the whole stage. The anopheles do not become infected till the autumn,

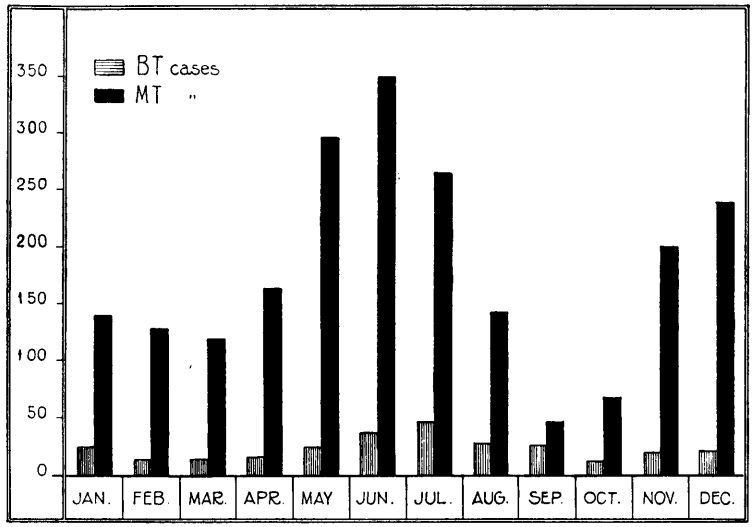


FIG. 24. SEASONAL CURVE OF MALARIA IN THE TROPICS.
Monthly incidence of malaria species in 5,000 labourers on a sugar plantation in Cuba.
(*After* Nedergaard, 1921)

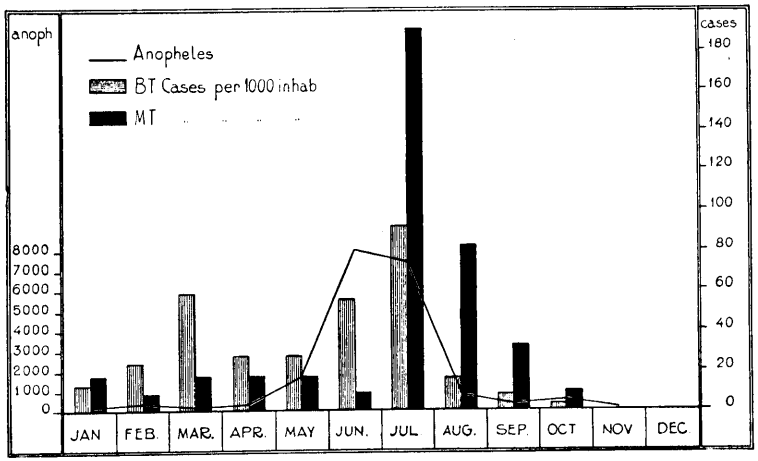


FIG. 25. SEASONAL CURVE OF MALARIA IN THE SUB-TROPICS.
Monthly incidence of malaria species and anophelines in the town of Posada, Sardinia.
(*After* Missiroli, 1930)

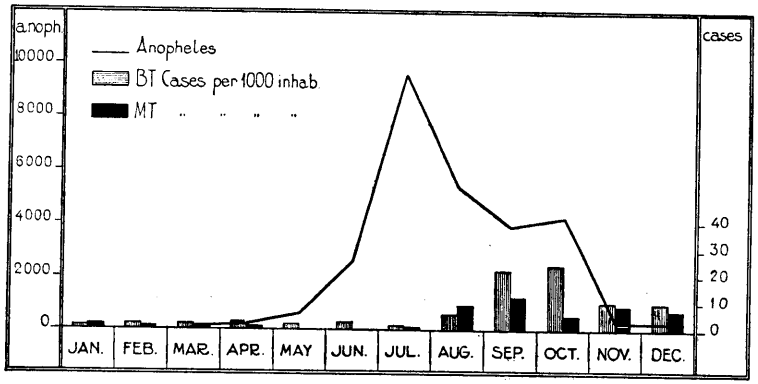


FIG. 26. SEASONAL CURVE OF MALARIA IN THE SOUTH TEMPERATE ZONE.
Monthly incidence of malaria species and anophelines in northern Italy (Venetia).
(*After* Missiroli, 1933)

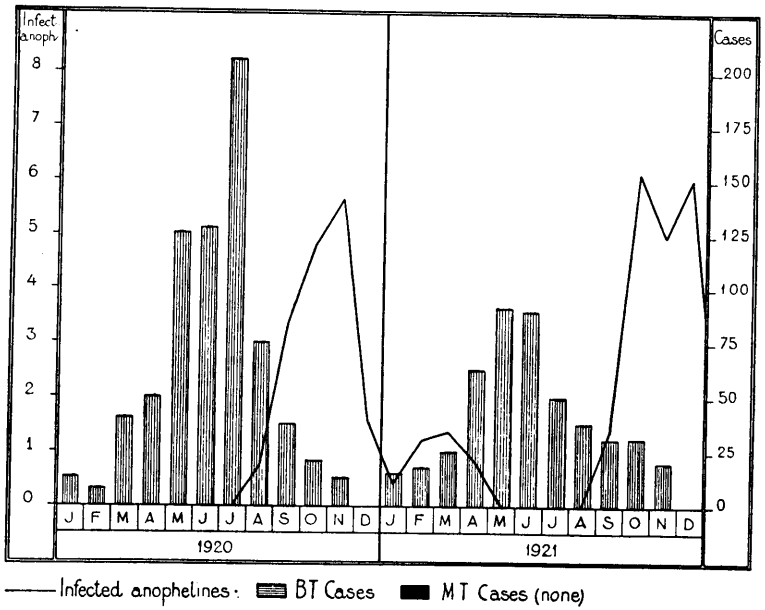


FIG. 27. SEASONAL CURVE OF MALARIA IN THE NORTH TEMPERATE ZONE.
Monthly incidence of malaria species and infected anophelines in North Holland.
(*After* Swellengrebel)

and the cases which they produce lie over, like wheat, to germinate in the following spring.

Man, the third party to this business of malaria transmission, is not as fortunate as the other two in his reactions to the annual pause. His system of defence becomes disorganized during the winter, for its efficiency depends entirely on constant stimulation. A native in Nigeria can remain in relatively good health while he is being infected almost every night, but if the rate of infection were reduced or interrupted for a long period he might not do so well. Even in temperate climates the end of each malaria season finds the collective immunity in a malaria zone very high. This is not achieved so easily as in the laboratory. There are three species of parasites and an unknown number of strains without any cross-immunity to speak of among them. Instead of the tolerance rapidly built up in a general paralytic patient for the single strain with which he has been heavily inoculated, we have the condition of chronic malaria characterized by a fluctuating anaemia and an increasing spleen which is the lot of the ordinary inhabitant of any small Sardinian village. Only by chance is he infected twice in succession with the same kind of parasite, and his individual malaria season draws to a close only when he has solidified anew his resistance to the principal strains which are in the air around him every night.

We have no idea how many strains of each parasite there are in any one locality. Sinton was able to isolate seven strains of *P. knowlesi* in a very short time from monkeys caught in Malaya. But to bring the malaria season to an end it is not, of course, necessary for every inhabitant to become immune to every one of the strains. They are already partially immune to many of them through previous infections, and only the children born during the winter have to confront each approaching summer without any protection at all. Even this may not be quite true. It seems reasonable that strongly immunized mothers might be able to transmit

passive immunity to their infants with their milk during the first year of life. This sort of congenital immunity has never, I believe, been investigated. Barber found a much smaller percentage of infants in West Africa infected in the early months of life than he had expected from the high sporozoite rate and great density of the anophelines. But these were blacks, and perhaps the babies enjoyed a racial rather than a transmitted passive immunity. At any rate, the inhabitants of our Sardinian village by August or September reach a point where a sufficient number of people are immune to a sufficient number of plasmodium strains to cause the epidemic to subside. For it is probably group immunity rather than the advent of winter or the disappearance of anophelines which brings to a gradual close the annual wave of malaria in hyperendemic areas of the sub-tropics. 'Hyperendemic' always implies an exceptionally high rate of malaria transmission, and so a correspondingly rapid immunization. It is possible that the epidemic might peter out more slowly if the malaria were less intense (Fig. 28).

The mechanism is revealed, however, by an experiment which we carried out in two Sardinian villages, Posada and Torpè, situated close together and exposed to the same conditions of intense malaria transmission.[1] In one of these (Torpè) it was found possible to treat practically every one of the thousand inhabitants with 2 centigrammes of plasmoquine twice a week, beginning in April with the first mosquitoes and continuing the treatment until the end of July. The other town was kept as a comparison area. Our treatment was very successful, for after the usual relapses in April and May we did not have a single case of malaria in June, and there was no infection among the anophelines. Thus we were able to observe a very curious contrast between the two villages, for in Posada the annual malaria epidemic took place as usual with its peak in July, whereas

[1] Missiroli, A., *L.o.N. Hlth. Org. C.H./Mal./*196, Geneva, 6 Mar. 1933.

in Torpè the whole epidemic was postponed two months, reaching its height only in September. It would seem that in the untreated village the curve of malaria began to fall in

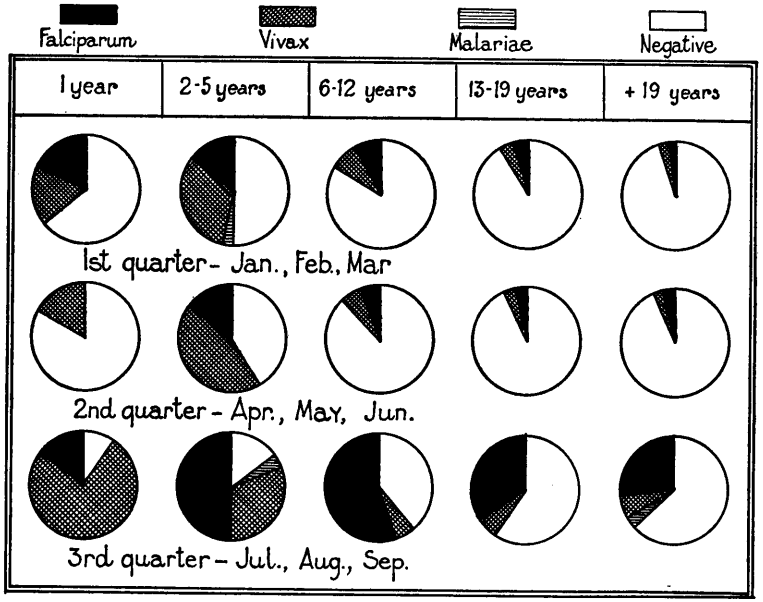


FIG. 28. RELATIVE OCCURRENCE OF THE SPECIES OF PLASMODIUM ACCORDING TO SEASON AND AGE-GROUP.

Quarterly blood examinations of the population of Posada in 1930. Note how the babies in the third quarter show more *vivax* infections and the older groups more *falciparum*, while the percentage of demonstrable infections decreases with age.

August and reached a low level in October, not because infected anophelines were lacking during that period, but because the population had acquired a certain degree of resistance to the strains present in the area. It is probable that at the end of July the community reached the immune condition characteristic of the tropics throughout the year. The inhabitants of the treated village, however, were as receptive at the end of July as those of the untreated village at the beginning of June, and the epidemic followed its natural course through the succeeding four or five months

at a time when the 'season' was over for the rest of Sardinia (Fig. 29). In the next year the malaria, untreated, returned to its normal schedule (Fig. 30).

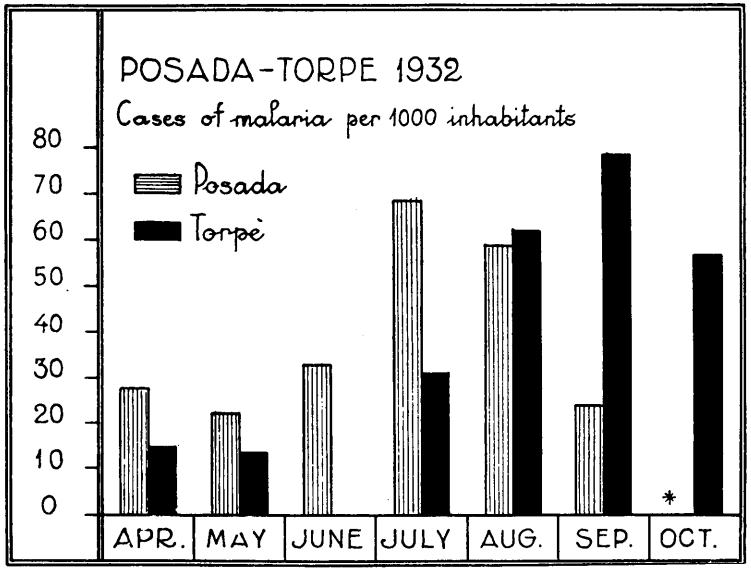


FIG. 29. A MALARIA SEASON POSTPONED TWO MONTHS BY PLASMOQUINE.

* Unknown.

This is confirmed by the late autumnal epidemics which take place in large aggregations of northern labourers who have sometimes been brought to highly malarious areas in Italy, on the supposition that malaria transmission was over for the year, since the local inhabitants were at the end of their annual epidemic. In such aggregations malaria may rise in September and reach its peak in November or December, falling to a low point again only in the early months of the following year.

In September, in our endemic village, tolerance is high, but by the next June the group is again receptive, especially the younger people. Each year the immunity must be built up again like an annual plant. This is easiest and more lasting with *vivax*. In the sub-tropics benign tertian is a

disease of early childhood; it is infrequent between the ages of twelve and nineteen, and it is rarer still among the adults.

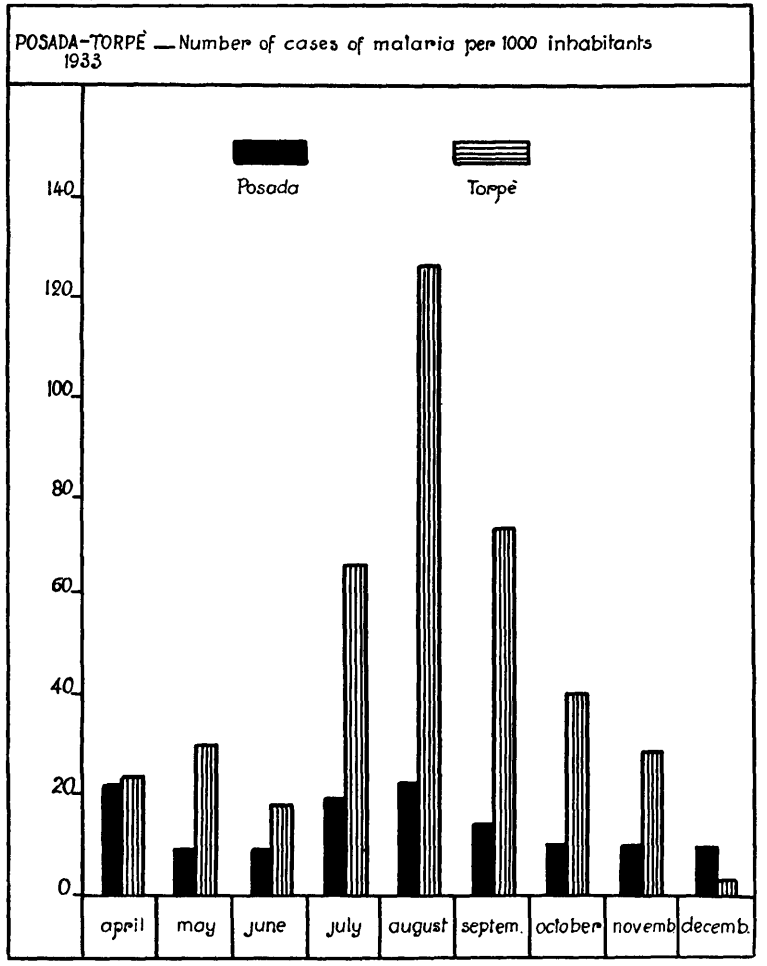


FIG. 30. NORMAL MALARIA CURVE IN POSADA AND TORPÈ IN 1933.

Vivax infections obtain a flying start every year because of all the hibernating infections which hail the advent of spring with a relapse, but it is a fire which soon burns out. Accumulated immunity renders most of the fuel incombustible.

Falciparum takes a much longer time to gather its forces, but the population, especially in the older age-groups, is more susceptible. There is a great dearth of *falciparum* gametocytes, but a sufficient number of anophelines can usually find them when doctors fail, and then they begin to increase by geometric progression. Covell and Bailey[1] calculated in an epidemic in Sind that one gametocyte carrier in two hundred inhabitants in the first week increased to a hundred by the ninth week under favourable conditions of spread. Once started, *falciparum* is more virulent, increases more rapidly, encounters less specific resistance, and produces many more gametocytes than *vivax*.

Each year *vivax* and *falciparum* epidemics pass in successive waves over the population, already inundated to a certain level with chronic endemic malaria. The constancy and depth of this permanent endemicity, determined by the regularity and frequency of infection, measures also the collective resistance of the community to the effects of seasonal parasitic invasions. But this constantly replenished tolerance to malaria, which we have likened to a sea, is subject to tides which rise and fall over periods of years, as these are favourable or unfavourable to anopheline production. When the tide of immunity is at flood it greatly dampens the superficial epidemic disturbances, but when it is at a low ebb the annual waves may be disastrously high. The height of the epidemic, in other words, varies inversely with the depth of the endemic malaria.

The true distinction, therefore, between endemic and epidemic malaria is not to be found in factors such as the virulence of the parasite or the density of anophelines. It lies in the resistance the population can muster to meet local variations in the transmission rate. We are forewarned by fluctuations in the spleen mass of the population, first studied quantitatively by Christophers in India, and applied

[1] *Rec. Mal. Surv. Ind.* 3 (2): 279, Dec. 1932.

by Gill to the prediction of epidemics. High anopheline densities will not produce a major disaster in the face of a considerable mean splenic enlargement. But if there is no accumulated reserve for defence the situation is ripe for an epidemic, and not much residual malaria is necessary to start the process. In the absence of any organization for protection a very small fire may end in a large conflagration. St. Croix,[1] one of the Virgin Islands, reported only 15 cases of malaria between 1918 and 1930—all, with one exception, immigrants from Puerto Rico—but in 1931 came a rainfall 24 inches above normal, leading to an epidemic of over 900 cases with 22 deaths. A similar event has recently occurred in Italy during the draining of the Lake of Nemi for the recovery of the sunken barges of Caligula. This little castle town in the Alban Hills had never had any malaria within the history of man, although without doubt there were always occasional visitors from the Roman Campagna harbouring the parasite. In 1928 the water-level of the lake was gradually lowered by pumps, exposing a marshy area near the village, and in 1929 in a population of 1,180 there were 616 cases of malaria.

The extent of such a disaster in Europe would seem to depend only on the size of the population, the production of man-biting anophelines, and the level of communal immunity. Hirsch,[2] in his *Handbook of Geographical and Historical Pathology*, describes pandemics of malaria in Europe in the past. Nevertheless, there is no reliable history in modern times of great regional epidemics such as those reported from northern India. The single exception occurred in Russia in 1922 and 1923, but the picture reveals an extraordinary background of calamity. After the retreat of 1916, the Russian people, pushed to the limit of human endurance by epidemics of cholera, typhoid, and dysentery, by famine

[1] Shaw, E. B., *Science*, **76** (1981): 566, 16 Dec. 1932.

[2] Cited by Gill from a translation by Creighton, C., New Sydenham Society, vols. i, ii, iii (1885).

and revolution, fell a victim to typhus as it had not been seen since the Middle Ages.

'There are no words', says Zinnser,[1] 'to record the dreadful sufferings of the Russian people from 1917 to 1921. The disease increased steadily and rapidly. . . . From the careful and conservative calculations of Tarassewitch, it is likely that, during these years, there were no less and probably were more than twenty-five million cases of typhus in the territories controlled by the Soviet Republic, with from two and a half to three million deaths.'

On top of all this there was in store the greatest malaria epidemic of modern times in Europe. In the middle Volga basin there had been an almost complete lack of rain for two successive years. The crops suffered the first year and in the second year they were destroyed. All the domestic animals died, either from lack of food or because they were sacrificed to the hunger of the population. Great masses of the people emigrated to more fortunate regions, where they became infected with new kinds of malaria, and in the meanwhile the immunity of those who stayed at home fell to a low level. The following year a great flood of the Volga inundated kilometres of plain along its left bank, and the receding waters in the summer turned all the depressions in the steppes into marshes which persisted throughout the breeding-season. On this physically reduced population, destitute of any biological defence either of domestic animals or of acquired immunity, descended the hordes of the anophelines, and to add to the tragedy returning emigrants, who had heard that the land was again productive, brought their new parasites. This is the nearest approach we have had to one of those notorious epidemics characteristic of the Punjab, of which Gill writes:

'There are few reliable statistics recording prevalence of sickness in epidemics, but few inhabitants escape, so that all business becomes suspended, railway services disorganized, food supplies maintained with difficulty. Many die for lack of food and attention, and in the

[1] *Rats, Lice and History* (1935).

small villages it is difficult to find a single individual capable of tending the cattle or ministering to the sick.'

In two months, during the epidemic of 1908, there occurred in the Punjab a quarter of a million deaths over and above the normal death rate. Such a situation, like the seasonal epidemics which rise to a peak in the summer of each year, is due to the unbalanced forces of infection and communal immunity coming, through more or less explosive interaction, to periodic equilibrium after an interruption of transmission. The gravity of the event is proportionate to the amount of imbalance. It is not necessary, as Christophers has pointed out, to presuppose the intervention of new factors such as the prevalence of a strange anopheline or the exaltation of a local parasite. The severest epidemic is only an exaggeration of the normal seasonal wave of malaria. But great differences in potential between infection and receptivity are not created merely by the usual winter pause in malaria transmission; they depend on that other characteristic of temperate climates, the fact that they may deviate strangely from normal expectation for years on end. A series of dry summers in Italy or the Balkans can reduce anopheles production and with it the infection rate to a low level. Suddenly the conditions may be reversed, as the capricious climate swings again to the other extreme to fulfil its obligation towards the forty-year average, and an overproduction of anophelines finds the population drained of its accumulated store of resistance, a victim of its own temporary well-being.

In his *Genesis of Epidemics* Gill has pointed out several features which seem to be peculiar to epidemics of this kind.[1] In the first place they can occur only in the unstable climates of the temperate and sub-tropical zones, in malarious areas subject at times to inundation as the result of

[1] 'Regional' epidemics are to be distinguished from 'local' epidemics caused by introducing non-immunes (such as soldiers, colonists, or labourers) into an endemic area. Localized epidemics may take place anywhere.

excessive rainfall and the overflow of rivers. 'Thus they do not occur in the tropics, even in those countries where endemic malaria is notoriously intense.' Secondly, they are separated in the same area by periods of at least five years, which is the time necessary for the immunity to subside. And finally, they are only as widespread as the combined climatic and anopheline factors which determine them. They break out simultaneously over the whole area, not spreading from any recognizable foci, and this is natural, for they arise from a residual malaria already thoroughly disseminated. They cannot invade contiguous regions in which the epidemic conditions are not present, and this imposes upon them a static character not often recognized. Thus the Soviet Commissary of Health (quoted by Gill), in describing the Russian epidemic, said that 'malaria in epidemic form has *spread* from Turkestan and the eastern provinces of Russia throughout the whole of central and northern Russia where until the last few years malaria was unknown'. But in the first place malaria of low intensity must have been present previously over the whole area, and secondly, as Gill points out, 'all so-called pandemics are probably stationary regional epidemics rather than the result of the rapid *diffusion* of disease, impossible to malaria. There is no unequivocal instance on record of malaria spreading in epidemic form either to the tropics or to non-malarious countries in the temperate zone.'

In October 1934, in apparent contradiction to Gill's fundamental thesis, a malaria epidemic of the first magnitude broke out with characteristic abruptness in south-western Ceylon—the only notable instance on record of such an occurrence in the wet tropics. The same mosquito, *A. culicifacies*, which has been responsible for all the great epidemics of northern India in years of excessive rainfall, was also the cause of the Ceylon epidemic, although this occurred in the midst of a prolonged drought. The paradox itself furnishes the clue to a reasonable explanation, which

is borne out by such observations as were made at the time. *Culicifacies* breeds intensively only in standing water, and while in the dry Punjab the proper conditions occur as an aftermath of floods, in the well-watered regions of Ceylon they are produced by drought, which partially dries up the rivers and greatly reduces their flow. There seems to be nothing mysterious or contrary to accepted theory in this epidemic. It occurred according to rule, in a relatively non-malarious and hence non-immune population, when a climatic freak permitted an extraordinary multiplication of dangerous anophelines by transforming the numerous flowing streams into chains of disconnected pools.

Colonel Gill himself, who has never given much weight to the density of anophelines *per se* in the genesis of epidemics, is far from satisfied with this explanation. He has deduced, from the dispensary records, that the epidemic began very suddenly indeed—in fact, almost on a given day. There was an outburst of cases almost everywhere on 27 October, without warning, and he is unable to believe that the epidemic could have been built up out of scattered small foci by the anopheles, however numerous. Furthermore, these first attacks were not associated with the expected mortality among young children. He suspects that they were not new infections and that the epidemic began as a wave of virtually simultaneous relapses in all the infected elements of the population, which in turn infected the anopheles *en masse*. This is the sort of thing which happens every spring in Sardinia and the Balkans, or even more characteristically in Holland, but simultaneous recurrences presuppose an equal number of infections taking place at about the same time some months previously. In default of these, the influences which might produce relapses in a widespread population all at the same time are rather obscure. Gill suggests a possible inherent periodicity of five to ten years in the parasite, or more probably a combination of certain meteorological conditions tending to recur at intervals of

years, such as might conceivably be related, let us say, to the appearance of sun-spots. Claus Schilling, too, once expressed the idea that an unusually high relapse rate might be the necessary prodrome of an epidemic, implying a possible increase in the virulence or infectiousness of the parasite. The feeling is indeed rather widespread that the explosive character of malaria epidemics involves something more than a susceptible population and an increased number of insect vectors. Epidemics of any disease seem in fact to develop a sinister character which tempts observers to assume either an unusual susceptibility on the part of the population produced by famine, economic stress, &c., or a change in the infecting organism due to increased frequency of passage or to some environmental influence.

The argument recalls the quandary we have mentioned of the malariologists of twenty years ago faced with the problem of explaining the annual summer outburst of *falciparum* malaria in the Roman Campagna. 'How to explain', said Bastianelli, 'the great prevalence of estivo-autumnal fevers in the beginning of July when in June the only cases on which the anophelines could have infected themselves had, for all we could see, only tertian parasites?' Caccini (1902) wrote that several observers in Italy had noted the absence of crescents when the new malaria season was imminent, and that he himself had never found crescents in that country from April to June. Yet quite suddenly in July the epidemic would break out with explosive violence, simultaneously over a wide area. We no longer resort to any influences more mysterious than summer heat, an abundance of anophelines, and a few good infectors carried over from the previous year, to explain this phenomenon. Mosquitoes, plasmodia, and new infections increase by geometrical progression, and, as I have remarked before, the peculiar character of such a curve is that, no matter how slowly it begins to rise, it soon shoots upwards almost perpendicularly and soars in no time to fantastic heights.

The annual *falciparum* epidemic in Italy occurred quite regularly, and the date of its appearance could be predicted almost within a week, yet it always managed to escape observation until it was in full bloom. No wonder, then, that an epidemic of malaria, taking Ceylon completely by surprise, was already getting beyond control at the time it was discovered. On a smaller scale this is constantly happening. The draining of the Lake of Nemi caused no malaria to alarm the health authorities until they were suddenly faced with an outbreak affecting a considerable percentage of the population. The urgency for administrative action in such cases usually precludes any intensive scientific study of the epidemic until it is over. The data, secured in confusion by an improvised personnel, will then be found to sustain the most contradictory theses in a post-mortem analysis.

Why do not regional epidemics take place in Europe? 'Exaggerations of the normal annual epidemic situation' are actually occurring at fairly regular intervals throughout southern Europe. Celli noticed that the waves of increased malaria endemicity in Italy occur every five or six years, and he mentions peaks in 1887, 1891, 1895, and 1900. As early as 1900 he suggested that epidemics of malaria might be due to the periodical development and exhaustion of malarial immunity, though he thought this might be the result of a biological modification of the parasite. In my own experience in Italy we have had epidemic waves in 1924, 1929, and 1936. The malarious years have wet springs and hot summers. Rain helps the anophelines and high temperatures the parasites. But the intervening years, though milder and drier, have a fair amount of malaria transmission too. In the Punjab, where there is practically no transmission in the inter-epidemic period, the annual immunity is virtually gone in five years. Gill reports one village which in 1908 furnished a spleen index of 77 per cent.; in 1913 this had fallen to 10 per cent. and in 1914 to 1·4 per cent.

Such a village is then ready for an epidemic, which will be precipitated by the next year of increased rainfall. In the Mediterranean basin such extreme variations are never seen, except possibly (and rarely) in parts of Spain. The inter-epidemic transmission, and hence the average resistance, never falls so low. The picture is one of an endemicity which fluctuates but never fails, with periodic epidemic exacerbations—a situation known in Greece as *endemo-epidemic* malaria. In northern Europe, immunity is always nil, but no amount of anophelines such as those which occur there can push the inoculation rate to dangerous levels. Such carriers as *messeae*, *typicus*, and even *atroparvus* never achieve the contact with man which an epidemic requires.

It has seemed to me that in western Spain we have the nearest European approach in climate and variable endemicity to the conditions which might be called potentially epidemic on a grand scale. The country is dry but subject to floods, transmission is normally at a low level but there are years of high anopheline density, and spleen rates may show rather ample variations. The stage seems continually set for an epidemic which never appears; or rather, there are many little epidemics but only one that I have heard of which seems to have lived in story. Pittaluga relates the case of a village where malaria one year was so bad that all the labourers were attacked. They were divided into two groups, each group working on the day they had no chill and resting at home next day with fever! This indicates the tertian type of the infection and the reduced state of the immunity, but it is not a very terrifying picture. Infections in Spain are widely spaced in general, so that it is not likely that a given individual will be infected more than once every two or three years. Even at this rate one-half to one-third of the population may theoretically come down with malaria annually, with the severe clinical symptoms which are to be expected in non-immunes. The malaria picture is one which at the height of the season would certainly cause

concern to a health officer, but examinations of blood and spleens in winter are in many localities completely negative. Most of the cases have time to recover from one infection before they contract another. We may call such a situation 'hypo-endemic', for, while the malaria must be carried over from year to year in the population, it is lost to sight in the inter-epidemic periods. It is in such situations that treatment seems to work wonders and appears, though deceptively, to prevent the spread of malaria. Every year, regardless of treatment, the epidemic is repeated. But this epidemic is never a great epidemic, and the reasons are essentially two: the rainy season is not the season of transmission, and the anopheline is that same *atroparvus* which wherever it occurs is a potential trouble-maker, but never, in the presence of even a modicum of live stock, a dangerous criminal like *elutus* or *labranchiae*.

The thing which characterizes temperate climate malaria is that the immunity factor and the infection factor are continually getting out of balance. This occurs every winter when transmission is interrupted, but to a more dangerous extent when the vagaries of the climate check anopheline production over a period of years. Equilibrium can only be restored by a wave of epidemic malaria. The infection-immunity balance of a malarious community is very much like that of an infected individual. It is not to be imagined as a pair of scales with infection in one pan and immunity in the other, for the immunity is a function of the infection —an organic opposition like that of a muscle resisting a thrust and not at all like that of a dam holding back water. The organic barrier restraining malaria develops its strength from the pressure put upon it. As the water rises, the dam becomes thicker, and in a flood it will deepen its foundations and raise itself in height. But if the pressure be relaxed the organic resistance weakens rapidly and inevitably just as a muscle atrophies when it has nothing to do.

In the individual a latent period in a malaria infection ends, when the balance is upset, in a relapse. In the same way, in a village a period of decreasing endemicity ends abruptly in an epidemic. And as in the individual, while all three parasites are usually concerned in the infection, one dominates the picture depending on the season, the intensity of transmission, or the degree of immunity present to each species of plasmodium at any given moment. But the progressive atrophy of immunity over a number of years is faster in the village than in the individuals which compose it, owing to the constant removal of immunes and their substitution by a larger number of non-immunes through the natural phenomena of death and birth. Thus immunity is lost less rapidly in the individual and more rapidly in the community than it can be acquired.

IX

APPRAISAL OF A MALARIA SITUATION

When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge of it is of a meagre and unsatisfactory kind. LORD KELVIN

BARBER remarks that no one visiting the island of Cyprus would take it to be very malarious. In its midsummer aridity it lacks all those features commonly associated with the causes of an intense malaria infection. But Cyprus is not remarkable in this respect. Not long ago Carter[1] revealed what seemed an unusual situation in Ceylon.

'Perhaps the most interesting and striking result of the survey', he writes, 'is the extraordinary difference in the degree of malaria prevalence in the moist and dry zones of the low-country. In the moist zone the rainfall is heavy and well distributed throughout the year, the vegetation is luxuriant, and paludic conditions—permanent swamps, pools, rivers and streams, paddy fields, &c.—appear to be everywhere present; and yet the degree of malaria prevalence is surprisingly low. In the dry zone, on the other hand, the rainfall is much less heavy, and very dry conditions prevail throughout the greater part of the year, during which period little surface water is evident and circumstances appear definitely unfavourable for the spread of malaria. But, except in the northern portion of the Jaffne peninsula and in one or two other restricted areas, the whole of this extensive region is intensely malarious.'

The farther we look, the more of such examples we find. Of the Philippine Islands P. F. Russell says: 'The classical picture of a malarial marsh-dragon rising from low-lying miasmal swamps is completely wrong as far as this country is concerned. Here malaria is found only in the attractive hill country fed by fresh running water from mountain streams; the flat land, high or low, is never malarious.'

[1] Ceylon Govt.—Sessional Paper 7, 1927.

That medical officers of limited experience with malaria should be misled under such circumstances is not strange. The Philippine experience is so instructive and valuable to us all that, although I have mentioned it already, it is worth bringing up again because it was not an isolated instance, but an example of the reasoning by analogy which characterized the early years of malaria control everywhere. In 1898, at the time of the American occupation of the Philippine Islands, no one knew very much about the causes of malaria except that in the United States it occurred in the vicinity of swamps. The troops were naturally quartered in the hills at Fort Stotsenburg to avoid the marshy plain around Manila. The site of the fort, however, turned out to be malarious, contrary to expectation, and in 1904 Whitmore, on dissecting some anophelines, found a very heavy infection in a lot of *myzomia* (probably *A. minimus*) which Major Crosby, the post surgeon, discovered to be breeding in the streams near the camp. The report of this important discovery was buried in the Medical Record book of Fort Stotsenburg, and only recently resurrected by Russell.[1] In later pages of the same book he found 'stagnant water', 'pools', 'tin cans', 'bamboo joints' mentioned as 'breeding places for malarial mosquitoes'. In 1914 Walker and Barber[2] rediscovered the essential fact about the hill-stream breeders and published it, while Heiser, who was Director of Health from 1905 to 1915, has recorded the circumstance that he did not in these ten years discover a single clear case of autochthonous malaria in Manila or on the plain around it. So fixed, however, were the old conceptions, that even as late as 1921 (writes Russell) the annual report of the Bureau of Health referred to malaria as 'due to the continuous standing of stagnant water in the rice paddies and the thick vegetation surrounding almost every district and barrio'. Not until 1925 was any malaria control in the islands based

[1] *Am. Jl. Pub. Hlth.* **26** (1): 1, Jan. 1936.
[2] *Philipp. Jl. Sci.*, sec. B, **9** (5): 381, Sep. 1914.

definitely on this fundamental fact that the disease is carried by a stream-breeding anopheline found only in the foothills. And that Americans are still too restricted in their view is suggested by a recent medical report of the United Fruit Company which begins: 'Malaria is widely distributed throughout the tropical and sub-tropical world wherever the rainfall is sufficient to leave standing water in which anopheles can breed.'

Such preconceived notions about malaria prevent an unobstructed view of any new situation. 'The truth', said Darwin, 'will not penetrate the preoccupied mind.' These traditional ideas, like the proverbs about the weather, have only a local validity, but we take them with us wherever we go and give them a popular though groundless currency in every clime. Consider the word 'paludism', relic of an age when people believed in the noxious effluvia from marshes, and now irremovably embedded in our thought as well as in our language as a synonym for malaria. Names, once they can be made to stick, resist change and influence public opinion—witness the political candidate who was defeated because his opponents referred to him as a sexagenarian! People are even ready to attribute some mysterious quality to marshes which do not cause malaria. Reports are collected on deltas and special studies made of rice-growing areas which have attracted attention because they are malaria-free. It is just as extraordinary that malaria does not characteristically follow rivers in the United States, although everybody takes it as a matter of course. It happens in each case that there are no local anopheline vectors which breed in sufficient numbers in that type of water. But there are plenty of deltas, rice paddies, and rivers in the world which are the sources of the most intense malaria.

Sizing up a malaria situation by the eye is clearly to invite trouble. It is something like the matching of cases by medical students in a clinical amphitheatre. As each patient

is wheeled in, they look attentively for outward signs of disease resembling those of patients they have seen before, and often become very skilful in diagnosis at a distance. They miss, of course, all the atypical cases. Carried into practice, the method is dangerous enough in clinical medicine, but in malaria it is disastrous, and for the same reason: a large proportion of the cases depart from the supposed rule. The truth of the matter is, not that there are a great many exceptions, but that there is no rule. In every field of malariology 'matching cases' leads nowhere but to confusion. A mosquito, harmless in Java, is found to be the chief vector in the interior of Sumatra. A method of treatment unusually successful in India is almost without effect in Sardinia. The half-mile radius, sufficient for larva control in Malaya, has to be quintupled in the Mediterranean basin. A village in Spain, in which half the population is in bed with chills and fever in August, turns out to be less infected than a village in Africa where virtually no one has to abandon work on account of malaria at any time.

This is elementary knowledge to students of malaria, but not to government or even perhaps to all health officers. We still have to explain to the budget-makers why funds and personnel are always needed for further field studies in malaria, even though Ross himself used to assert that we knew quite enough to go ahead without delay on every front and eradicate the disease, since infection could come only through mosquitoes, and mosquitoes could breed only in water. The health officer must be able to convince the authorities that time, money, and lives can be saved by pausing to obtain a thorough knowledge of each individual problem before acting, as a physician takes time to make an accurate diagnosis before proceeding to treatment.

The first thing a health officer wants to know about his problem is how much malaria there is. Afterwards he can determine its causes and consider how to deal with them,

but he can do nothing until he has established a base-line from which to measure progress, and is in a position to contrast this malarious situation with some other which he may have chosen for comparison. To do this he will have to find some way of measuring malaria and of expressing the result in numbers. Now malaria marks its victims in four different ways: it produces a very characteristic fever, it causes anaemia by blood destruction, it fills the blood-stream with easily recognized parasites, and it enlarges the spleen, an organ so placed that when swollen it can be felt and its size estimated through the abdominal wall. With all these signs to go by it would seem that no malaria case could escape recognition. With a little effort the total amount of malaria in the community could be determined and the health officer would know where he stood at any moment.

Unfortunately, as soon as we begin to put this method into practice we run into an absurd difficulty. The four tests do not divide the population neatly into two groups, the malarious and the non-malarious, as we should like. They unexpectedly produce four different groups of people which partially overlap but somehow do not seem very homogeneous. Some have parasites but no fever, and some spleens but no parasites, and our net will have caught a number of apparently healthy persons looking quite out of place. It reminds one of the story of the police department which sent out four photographs of a badly wanted individual taken from different angles to make identification easy, only to receive a telegram from a distant city that they had three of the rascals in jail and were hot on the heels of the fourth. Let us examine these four groups to see what they mean and how they differ from one another.

The Group with Clinical Symptoms

Counting the sick is the statistical method usually applied to infectious diseases, and malaria with its characteristic

attack would seem to make such a census anything but difficult. In infantile paralysis it is possible that only one in a thousand infected children actually develops the unmistakable paralytic signs of the disease, but with malaria, even if the symptoms are occasionally puzzling, the parasite can always be found during the acute stage in any drop of blood. Now while this is perfectly true of acute malaria, chronic cases carry their infections with less ostentation. They may present a general picture of poor health, but they will be up and about most of the time and for long periods may show no parasites in the blood. In epidemics of malaria the number of acutely ill people can be counted rather easily, but when the disease is more intense, when a large proportion of the population is infected so often that they never have time to recover from malaria, when, in other words, the situation becomes endemic, then curiously enough the amount of obvious illness decreases. A growing tolerance tends to suppress clinical manifestations, and acute attacks become infrequent. The Italian town of Sermoneta, for instance, located in the Pontine Marshes, was crushed beneath the weight of malaria for centuries. Like a heavily infested plant it had become dwarfed and infertile, unable to balance death rate with birth rate. All the children had enlarged spleens, half the babies were infected in the first year of life, and the population had been decreasing as far back as the records go. The whole population was examined in April 1924, but only a dozen persons—mainly children—had any acute symptoms. What seemed more characteristic was an appearance of anaemic depression hard to describe, and there were several cases of malarial cachexia, now rarely to be seen in Europe, a condition of complete exhaustion of the natural powers of resistance to the infection. These individuals were without fever, but they were in a grave condition and derived no further benefit from treatment. There were also three persons with spleens so enormous that they could no longer carry them about. Apart from

this, no one seemed incapacitated or gave a history of recent chills and fever. One middle-aged man, with a spleen which filled half his abdomen, insisted that he had never had an attack of malaria in his life. It is evident that, although malaria is a notifiable disease in Italy, morbidity reports from a town like this have no value whatever and may be positively misleading. During the early years of larva control at Sermoneta a large body of non-immune labourers from north Italy were suddenly quartered on the community. Acute malaria at once flared up and gave the central authorities the impression that malaria had increased in Sermoneta, whereas, in fact, the transmission rate had probably never been so low. Authorities usually attribute incomplete notification of malaria to the negligence of the doctors. The Annual Report of the Department of Health in Palestine for 1934 remarks, for example, that 'the Arabs and Jews of the Huleh region, where 100 per cent. are infected, reported only two cases during the year'. The fact is, local physicians are at a loss what to report when the majority of infections are chronic. Death certificates help us even less. Thirty-seven people died in Sermoneta in 1925 (a death-rate of forty-one per thousand), but malaria was given as the cause in only three cases. Pneumonia, nephritis, tuberculosis, dysentery, and premature birth or congenital weakness accounted for 80 per cent. of the deaths. Yet the suppression of malaria transmission reduced the death-rate to twenty in less than ten years.

The survey of Sermoneta was carried out in the off season, but M. C. Balfour[1] has made several 'sickness' surveys in small villages in Greece covering a whole summer. In Vovoda, typical of the highly malarious communities, about 4 per cent. of the population, on the average, showed fever at the weekly visits, but only one in twelve of these had a temperature over 38° C. (100° F.). About 2 per cent. were incapacitated for work at any one time, and this for one

[1] *Riv. Malariol.* **15**, sec. 1 (2): 114, Mar.–Apr. 1936.

or two days only.[1] Carr, Mandakos, and Barber[2] surveyed a number of Macedonian Greek villages with the same results. In a 'highly endemic' village less than 2 per cent. were clinically ill at the period of maximum malaria. Contrast this picture with that of the American Middle West half a century ago, when malaria was undoubtedly severe and widespread. There are eyewitnesses who still remember times in Indiana when there were 'not enough well to take care of the sick', and a physician in south-western Missouri mentions being impressed by the fact that after midnight there would be a light in almost every home, showing the presence of a case of malaria. The evidence of all this acute infection leads paradoxically to the conclusion that the malaria was not really intense and, perhaps for this reason, soon disappeared from the northern Mississippi valley. For while acute clinical malaria increases with the inoculation rate up to a certain point, beyond this it sinks into chronicity, and the maximum of fever and disability will be caused by something less than the maximum density of the anopheline vectors. The *amount* of malaria, that is its incidence as measured by the number of infected persons, is one thing, and its *intensity*, or transmission rate as determined by the frequency of inoculation, is quite another. It is like money, the amount of which, economists tell us, is far less important to business than the velocity of circulation.

The Group with Anaemia

But if the clinical picture of malaria does not correspond with the intensity of infection, neither does the anaemia which it causes. Christophers found no correlation between

[1] MacDonald suggested that small degrees of fever might be a valuable index of malaria infection. He took the temperatures of over a thousand children of Freetown, Sierra Leone, and only 6 per cent. fell below 99° F. Unfortunately there was no comparison group to show that this was due exclusively to malaria (*Ann. Trop. Med. & Parasit.* **20** (3): 239, 13 Aug. 1926). [2] *Ann. Trop. Med. & Paras.* **29** (4): 399, 18 Dec. 1935.

malaria infection and anaemia in highly endemic areas in India, and noted that the heavily infected children appeared to be in a 'fair state of health after the first two years'. In the individual the blood picture is modified as time goes on by the growing tolerance to the effects of the disease, and in the community it is influenced by so many factors not connected with malaria that a normal standard hardly exists. As an index of malaria it receives little attention, for its implications are uncertain and require elaborate analysis. A trained microscopist can pick up indications of the degree of anaemia from the blood preparations which he is examining for parasites, and such a study could be included more often than it is in population surveys. The principal objection is that it is a condition not specific for malaria, and cannot stand alone as a mark of the disease. Like the death rate and the birth rate, the haemoglobin rate can be used, as Boyd suggests, to 'present concretely the general physical impairment of the community', but for all the epidemiological information it gives, it is hardly worth the trouble and expense of investigating.

The Group with Parasites

We have now arrived at the third group of malaria victims, those who have parasites in their circulating blood. Here we have to make a distinction at once. Some will be having an acute attack, and we understand why their blood should be full of parasites, but the others will be the so-called 'apparently healthy carriers'—people without symptoms whose activities are unrestricted by their latent infections, but who, quite unknown to themselves, have great numbers of the organisms in their blood at the time of examination. How this comes about we have to admit we do not understand at all. Acute attacks end with the removal of all the parasites from the circulation by the sensitized giant phagocytes of the spleen and other tissues. It is true that the parasites have refuges in the body where they

are safe from attack, but when they venture into the circulation they are at once mopped up by the watchful defenders. Or, if they succeed in making some headway, the fight is on again, with chills and fever, and the patient has a relapse. But fairly frequently the parasites are allowed to circulate freely in the body for a period, and even to increase their numbers up to a certain limit without molestation. It seems to take place almost by agreement; the dogs are called off, as it were, and no symptoms whatever result. This happens very often in individuals with enlarged spleens, so that it is evident that the reticulo-endothelial killing machine is ready but not functioning. Then one day the parasites are all gone again, slaughtered or bottled up somewhere out of sight, and discipline is restored in the body. Such recurring evasions of the parasite have been called haemic relapses, which does not of course explain them, and it is these which we pick up in a general blood examination of a malarious population. They are the result of previous infections, and, if we could interpret them aright, might give some useful information as to the past experience of the community with malaria. To avoid the complication of acute clinical attacks, which are always an inextricable mixture of new infections, reinfections, and relapses, it is better to look for healthy carriers in the winter, or at a time when no transmission of malaria is taking place.

The percentage of the population which has parasites in circulation at any given moment is known as the *parasite rate*,[1] but of course it can never be accurately determined even by the most careful microscopic search. Ross drew a distinction, therefore, between a *rate* and an *index*. The rate refers to the true situation as it exists in the population and should be confined to data which give us the whole

[1] A better term would be 'ratio', since rate is specifically a quantity or amount measured per unit of time, as birth rate, marriage rate, &c. However, the word has obtained wide currency among malariologists (Ross, Christophers, &c.) in the sense of a fixed relation of quantity between two things—a definition, after all, which is to be found in Webster.

truth, such as the exact birth rate or death rate. But where we judge by sample of the population or by inexact methods, or indirectly by some correlated phenomenon, the figure we obtain is an index, such as an index of prosperity, or a parasite index obtained from the examination of children only.

Now it is generally considered that the relative number of parasite carriers depends on the recent prevalence or diffusion of malaria. Thus the annual wave of new infections each summer will be reflected in the parasite rate of the following winter, and a great epidemic will leave its traces in the blood of the population for four or five years. In the Amritsar area, after the tremendous epidemic of 1908 in the Punjab, Christophers[1] found over half the population carriers in the following year, although the transmission was very low, and not until 1913 was the percentage again below ten, approaching normal. But these are epidemic conditions indicating a low level of immunity. A stiffening of the communal resistance through years of continued high malarial intensity will tend to restrict these apparently harmless excursions of the parasites into the peripheral blood and will cut down the number of carriers drastically. In the village of Sermoneta, which we have referred to before as an example of high endemicity, the survey of 1924 showed a general parasite rate of only 15 per cent., although every school child and 96 per cent. of the adults had enlarged spleens, and there was every reason to suppose that the population was 100 per cent. malarious. It is one of those indices which fail to accompany an increasing frequency of infection beyond a certain point. A very high and constant intensity and a rather low, fading intensity might even produce the same rate, and somewhere between the two would lie the conditions favouring a maximum of carriers. What is the meaning of the low rate in Sermoneta?

[1] *Sci. Mem. Off. Med. & San. Dept. Govt. India* (Calcutta, 1911), No. 46, new series.

Was it due to immunity, or did the transmission fall somewhat during the preceding summer, affecting the parasite rate before sensibly reducing the spleens? Had we data for several years running, we might be able to say, but to interpret a single survey we shall need additional knowledge.

One of the aids to interpretation of the parasite rate is the relative prevalence of the parasites or the extent to which each of the three plasmodium species enters into the general blood picture on the day of the survey. The gathering of this information is simplified by the fact that although mixed infections are general in the sub-tropics—and in Sermoneta we presume that every one of school age or older will have been repeatedly infected by all three parasites—only one will usually appear at a time in the blood-stream in sufficient numbers to be found by ordinary methods. Which one this will be depends on a number of things such as season of the year, the possible absence of other parasites, and mysterious geographical and other factors not well understood; but above all it depends on the state of relative immunity of the individual to each of the three species. *Vivax* seems more readily suppressed than either *malariae* or *falciparum*. In the Belgian Congo Schwetz[1] has examined thousands of individuals, and he finds that *vivax* is already rare in the blood-stream after three years of age and disappears completely at five; the quartan parasite (*malariae*) is rare after ten and disappears at fifteen, and after this age *falciparum* is the only species found. Furthermore, *falciparum* builds up its numbers more rapidly than *vivax*, produces more gametocytes to secure its spread in the community, and therefore will be favoured in every way by a high transmission rate. This should be reflected, of course, in the so-called parasite formula, or relative prevalence of the species, especially in the children. Here, for example, are some records, reported by M. C. Balfour, of the annual blood surveys of

[1] *Riv. Malariol.* **15**, sec. 1 (1): 60, Jan.–Feb. 1936.

the school children in Komotini, a Greek town of about 30,000 people:

Autumn of	*Malaria situation*	*No. exam.*	*Per cent. with parasites*	*Relative percentage of species*	
				Falciparum	Vivax *and* Malariae
1930	Low endemicity	650	9	60	40
1931	Epidemic	685	24	73	27

The evidence points to increased transmission and new infections, and in fact 1931 was a year of high malaria prevalence in Greece. Under such conditions *P. falciparum* appears to increase relatively to the other species.

In 1932 there began a series of mild years with reduced transmission, ending abruptly in 1935 with another general increase in malaria. All this was mirrored in the Komotini surveys:

Autumn of	*Malaria situation*	*No. exam.*	*Per cent. with parasites*	*Relative percentage of species*		
				Falciparum	Vivax	Malariae
1932	Moderate endemicity	692	15	68	27	5
1933	Declining endemicity	670	22	47	35	18
1934	Low endemicity	690	10	25	57	18
1935	Rising endemicity	681	18	59	13	28

Since *falciparum* infections are apt to be acute and of short duration, any spacing of inoculations reduces their frequency at once. Thus two dry summers were enough to reverse the relative positions of *falciparum* and *vivax* in the blood picture, and *malariae* was revealed as a factor of unsuspected importance. The behaviour of the quartan parasite is often baffling, but we know that it causes a resistant and long-lived infection. When fresh infections are at a minimum and the endemic is maintained by relapses, it is only reasonable to suppose that the proportional prevalence of quartan will be raised. If we arrange the parasites as above in the order of increasing persistency, we find that a lowered infection rate causes the percentages in the right-hand columns to grow at the expense of the left. In 1935 Komotini suffered from an increase in malaria which put *falciparum* in the lead again and in fact restored it at one bound to the position it had held in 1930. Thus the parasite *formula* is more sensitive, accurate, and informative than the crude *index*, which changes more slowly and always takes two or even three years to recover from an epidemic.

But if the natural oscillations of malaria can influence the parasite formula so decidedly, this ought to serve as an excellent indication of the success of anti-larval measures in suppressing transmission. Near Marathon is the village of Nea Makri, in which malaria transmission was practically abolished in 1932 by the sub-soil drainage of a large marsh.

Village of Nea Makri

Autumn of	*No. exam.*	*Per cent. with parasites*	*Relative per cent. of species*		
			Falcip.	Vivax	Malariae
1931	55	56	87	13	0
1932	57	21	33	50	16
1933	64	11	14	57	29

To judge whether this improvement was due solely to the drainage work or was in part owing to natural causes, we should consult the data from some comparable area in which nothing was done. We happen to have the figures from Marathon itself, where no measures had been taken against the anophelines.

Village of Marathon

Autumn of	*No. exam.*	*Per cent. with parasites*	*Relative per cent. of species*		
			Falcip.	Vivax	Malariae
1932	134	23	65	35	0
1933	120	17	30	65	5

The 'shift to the right' in the parasite species is more marked in Nea Makri than in Marathon, but we are warned, by the contemporaneous improvement in both places, that we must not attribute the results in Nea Makri entirely to antimalaria work.

Turning back a moment to Sermoneta, with its low parasite rate of 15 per cent., we find the following additional information:

Village of Sermoneta—April 1924

	No. exam.	*Per cent. with parasites*	*Relative per cent. of species*		
			Falcip.	Vivax	Malariae
Children under 12 .	270	33	28	57	15
Inhabitants over 12 .	500	5	34	50	16
Total . .	770	15	29	55	16

We suspect now that the transmission rate was not high during the preceding summer, but the enormous influence of immunity is shown by the fact that there were seven times as many carriers among the children as among the adults. The trend towards *vivax* was less marked in the older group because of a more developed resistance. To obtain a responsive index, as free as possible from the dampening effect of immunity, we must look to the children, and, in fact, modern indices are now derived entirely from the age-groups under fourteen, and in the tropics under ten.

It is clear that even school children will have begun to develop an immunity to the malaria parasites, and that our only perfect index of transmission will be furnished by infants in their first year of life. Babies are non-immune immigrants and dry fuel to the fire of malaria. They are not easy to treat and relapse constantly. An autumnal parasite survey may not find every infected baby, but such an *infant malaria index* furnishes the most accurate information we can have of the frequency of malarial infection during the preceding summer and of the relative incidence of the

different parasites. At Posada over half the infected infants showed *P. vivax*; in school children this species was not uncommon; in the age-group over thirteen years it was rare.

There is one more thing to note with regard to the data from Sermoneta. The index was taken in April, and this is the season at which we expect a wave of relapses from the *vivax* infections of the previous autumn. A third factor enters into the picture then besides immunity and low transmission—the season of the year. When *vivax* prevails in the autumn, that is important news; when it prevails in spring, it is less significant. It would have been better to take the index in February.

But there are a great many confusing factors about a parasite index. What are the causes which bring parasites into the blood without symptoms, and if it is a sort of relapse, what is its incubation period and its effect on immunity? Boyd suggests that the body may develop two kinds of immunity: one destructive to the parasite and the other resistant to its hypothetical toxins. Schilling believes that the parasite develops an immunity to the human carrier. Others regard the parasitic invasions as due to external causes: the weather, inter-current infections, exercise, food, or even the method of treatment used in the original infection. If we look again at the chart of fifteen cases facing p. 187, we can see that the particular time chosen for a general blood examination would make a great difference in the parasite rate. It is hard to believe that the phenomenon is wholly fortuitous, and yet, if the causes are internal, each carrier will have his own particular reason for having parasites in his blood at the moment of examination, and our index will represent an aggregation of chance encounters as accidental as meeting a railway train at a level crossing. But if the causes are external, they might influence the whole group and we be none the wiser. School children are sensitive to heat and cold, to fatigue and the effects of food. We do not usually inquire about

such matters in taking a parasite index. No wonder Boyd remarks that the blood picture of a community is the resultant of such complex factors that it would seem hopeless to find a law in the chaos of possible combinations.

One of the peculiarities of the carrier group which differentiates it from all the others is that the persons who compose it are never the same on two different occasions. Barber, Komp, and Newman[1] once examined the labourers on a banana plantation in Panama, all of whom they had reason to believe were infected, and found 47 per cent. positive for parasites; but on a resurvey, nineteen days later, only 39 per cent. of these positives still showed parasites, while 43 per cent. of the negatives were now positive. MacDonald[2] had almost the same experience in Freetown. He examined forty-nine school children and found parasites in only twenty-three the first time, but seven subsequent examinations raised the number to forty-two. Of the seven negatives remaining, two had enlarged spleens, four had temperatures above 99° F., and only one appeared to be normal. Thus an index of 47 per cent. meant in this case also that virtually all the children were infected. The two cases agree only by accident, for we saw at Sermoneta that children and adults exposed in an identical fashion to malaria and all infected give widely different results on a single examination. But multiple examinations would defeat the object of our survey, which is to record the presence of parasites in the community blood-stream at a given moment. Whether this moment is well chosen or not we have no way of knowing. It is much the same as trying to estimate the commercial activity of a port by counting the vessels at the docks on a given day. Each boat is there on its particular errand and we shall never see the same collection again. We may have hit upon a slack time, or a storm may have driven an unusual number to harbour.

[1] United Fruit Co. 17th Ann. Rept. for 1928, Med. Dept., p. 45 (1929).
[2] *Ann. Trop. Med. & Paras.* **20** (3): 239, 13 Aug. 1926.

We have to accept our index as we find it without much knowledge of the underlying circumstances, and make what sense of it we can. One thing at any rate seems fairly clear: the parasite index always greatly understates the facts. In that case, could we not multiply it by some factor which would give us a closer approximation to the truth? But we have just given some examples of totally infected population groups in Freetown, Sermoneta, and Panama of which the parasite indices were quite different, both in children and in adults. The factor evidently depends on the level of local immunity and its efficiency in suppressing the circulation of parasites. No one has yet given us a formula for estimating that.

The Group with Enlarged Spleens

The oldest method of measuring malaria is by counting the enlarged spleens. Dempster[1] hit on the idea in 1847. 'The spleen test', he wrote, 'forms an accurate method of estimating the salubrity of different localities, and its degree of enlargement is most probably indicative of the intensity of the remote cause of the disease.' What this remote cause was, no one was destined to know for another fifty years, but the test proved a sound one.

There are two kinds of enlarged spleen, as Christophers has pointed out: the soft spleen turgid with blood, acute and transitory, and the hard spleen caused by the mobilization of phagocytic tissue, slow to return to normal. Swellengrebel mentions an island near Java called Modjowarno, where the vector, *A. aconitus*, breeds only one month a year. The spleen index may be 50 per cent. in July and 4 per cent. in December. This is epidemic malaria, and these would be soft spleens. But in endemic areas there is a mixture of hard and soft spleens. The soft spleens will be found in the early age-groups and in those persons protected by fortune or by screens from multiple infections. Hence the

[1] Reprinted in *Rec. Mal. Surv. Ind.* **1** (2): 69, Mar. 1930.

spleen rate itself is a complex phenomenon, and to simplify our indices as much as possible we try to keep the chronic and acute spleens apart. It is not easy to distinguish them while new infections are taking place, nor are we so much interested in acute spleens if our object is to obtain an idea of the intensity of the malaria. It is the spleens which persist, in winter, in apparently well individuals which measure the extent of immune reaction to infection. They do not measure the immunity itself, for a spleen may diminish in size with the establishment of a polyvalent immunity. They indicate *en masse* precisely what we wish to know, namely the intensity of the malaria to which the population has been previously exposed.

Chronic malaria with persistent, hard spleens seems impossible to produce in the laboratory. Endemicity requires superimposed infections with different species and strains of plasmodium. These are very stimulating to phagocytic tissue, which builds itself up to meet the multiple attack. The size of the spleen is an index of the response of this tissue, and the splenomegaly is persistent. Great epidemics may raise the normal spleen rate for years. In endemic areas, in spite of the long interruption of transmission in winter, individuals are still handling old infections when the new crop comes in. The winter spleen then, and not the summer, is the best measure of previous malaria intensity or transmission rate.

There will be overlapping of infections even with low endemicity and relatively infrequent inoculations, for infective bites are never evenly distributed. Christophers has pointed out that if one hundred infections were distributed completely at random among a hundred individuals,

37 would escape infection
37 would get 1 infection
18 ,, 2 infections
6 ,, 3 ,,
2 ,, 4 or more.

The infection rate is only 63 per cent., but there will already be a nucleus of individuals who have been infected two or more times in rapid succession and will be building up hard spleens. If the inoculation rate is now pushed up to such a figure that half the population acquire hard spleens that last through the winter, few individuals will entirely escape infection. The incidence of malaria can go no higher, of course, than 100 per cent., but the intensity of infection may still increase almost indefinitely, bringing about what is known as a *hyperendemic* situation.

The distinction between endemic and epidemic malaria lies in the intensity and persistence of the infection in the population rather than in the regularity or stabilization of the conditions favouring transmission. Malaria is endemic in the Balkans, but transmission is completely interrupted for six months or more every year. The difference between a Spanish and a Macedonian village lies in the resistance the community builds up and carries over into the following year. The infectivity of a community is shown by the acute infections, and it is correspondingly high if the endemicity is low. Epidemic malaria, then, is the malaria of non-immunes, and endemic malaria is that which is of sufficient intensity to create and maintain an effective and continuous immunity from year to year as revealed in the splenic index. We may look upon endemic malaria as a sea of overlapping and persistent infections, which has its rising or falling tides as the years are favourable or unfavourable to a high transmission rate. This sea is subject to epidemic waves and surface storms, and the shallower the sea the more imposing are these waves. In many parts of Spain, for example, the waves seem to be everything, and we cannot measure the depth of the constant endemicity because we cannot detect the slight enlargements of the spleen or find parasites unless they are present in considerable numbers, and this is the condition we call hypo-endemic. In the Balkans the seasonal waves are still very striking, although

there is always a sufficient endemicity to prevent disastrous epidemics. In the tropics the sea is very deep and the waves of relatively small importance. Such a situation, if at least half the population is found at all times with hard spleens, is called hyperendemic.

The spleen index, like the parasite index, we limit by preference to children, and for the same reason. After a certain age in any endemic region immunity will begin to influence the size of spleens and cut down the numbers. When adult spleens are measured, therefore, they should be recorded separately. In the Jalpaiguri Duars, Sarkar[1] found the maximum number of palpable spleens among the two-year-olds, and in the Chittagong Hill Tracts, at the age of three.

Development of immunity as shown in spleen indices

	Spleen indices	
Years of age	*Jalpaiguri*	*Chittagong*
1	80·7	76·6
2	87·6	84·0
3	86·1	85·3
4	85·0	79·2
5	83·2	75·6
10	63·1	43·8

In Europe the maximum splenic reaction to infection comes much later—at nine years or more. It is an excellent point to determine. It indicates the comparative intensities of malaria in different regions. Under epidemic conditions, however, the spleen rate of all age-groups, including adults, will be fairly uniform.

The index tells us the number of enlarged spleens but little about their size. It is true that number and size are correlated to a degree, and the higher the rate the larger will be the spleens, but the results of malaria control will often be more accurately reflected in the diminishing volume than in the diminishing number of spleens. Spleen sizes

[1] *Rec. Mal. Surv. Ind.* **3** (2): 197, Dec. 1932.

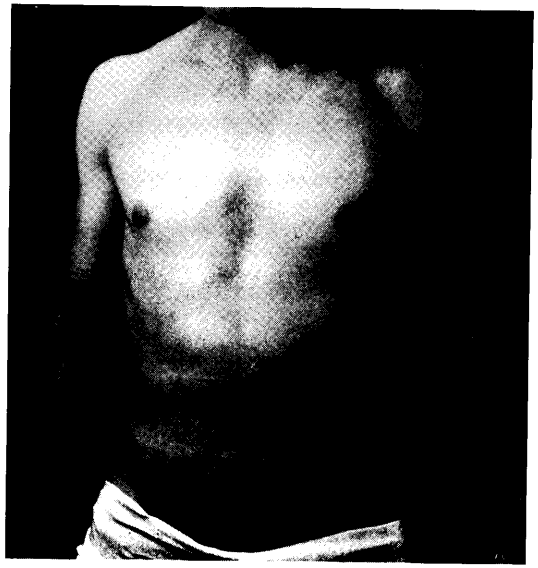


FIG. 31. METHOD OF RECORDING THE POSITION OF THE SPLEEN

are recorded in ordinary practice by noting where the lower border lies in the abdomen, and this is called the 'position' of the spleen. The different classes are numbered as in Fig. 31. No number is given to the spleen which can momentarily be felt when the patient forces it below the margin of the ribs by a deep breath. This spleen is called 'P' or palpable on inspiration only, but there is a whole category of slightly enlarged spleens which cannot be felt at all, so that no line can be drawn between the 'negative' (O) and the 'palpable' (P) spleens. These two classes are often combined and considered 'not necessarily malarious'. As a matter of fact Dionisi, one of that famous group of Italian pathologists who built up much of our knowledge of malaria, considered that a spleen must be enlarged to twice its normal size before it can be detected. The old method of using finger-breadths to measure the projection of the spleen below the ribs has now almost disappeared. The only rational way of comparing the spleen of a child with that of an adult by that method is, as Grassi suggested, to use the patient's own fingers to measure his spleen. The more painstaking method of Christophers,[1] who uses a tape-measure and a correction table, is too accurate for ordinary field work, whose object is not to study the effect of malaria on the spleen, but to measure progress in control. The method illustrated in the diagram, based on an idea of Schüffner's,[2] is the one now used over practically all of Europe.

When the malaria transmission rate remains low for a number of years, the effect is immediately apparent on the average size of the spleen. Dr. M. C. Balfour has kindly furnished me with the following record of the Greek village of Nea Carvali, where all bedrooms were mosquito-proofed in 1932, and in addition a series of dry years greatly reduced anopheline breeding.

[1] *Ind. Jl. Med. Res.* **11** (4): 1065, Apr. 1924.
[2] *Meded. Burg. Geneesk. Dienst. Ned.-Ind.*, No. 9: 1, 1919.

Nea Carvali—Spleen and infant malaria indices during a period of lowered transmission

(bedrooms screened in 1932)

Autumn of	*No. exam.*	*Spleen index*	*Per cent. of spleens*					*Average spleen*[1]		*Infant malaria index*
			0	*P*	*1*	*2*	*3 & 4*	*Value*	*Position*[2]	
1930	88	100	0	3	15	40	42	4·2	3	..
1931	100	100	0	3	5	53	39	4·3	3	47
1932	90	100	0	6	22	60	12	3·8	2	8
1933	106	93	7	13	37	29	14	3·3	2	6
1934	107	82	18	24	31	22	5	2·7	1	2
1935	84	63	37	30	20	11	2	2·1	1	0

This modern method of spleen analysis lends itself easily to graphic exposition, so important an aid to our understanding of a situation. The graph opposite (Fig. 32) illustrates a simple method of handling such data. The spleens, yielding to the effects of a low rate of transmission, have ended by arranging themselves in the descending order of magnitude which we may take to mean a decreasing as contrasted with an increasing or stationary intensity of malaria.

Spleen and parasite indices are a rather surprising development in the measurement of an infectious disease. Instead of counting the sick, which seemed logical enough at the outset, we end by examining only those who show no acute symptoms, in the non-malarious period of the year,

[1] The position of the lower border of the average spleen is found by assigning an arbitrary value from 1 to 5 to each class of spleen, and obtaining a weighted average as follows:

Nea Carvali, 1935. Position of the average spleen:

Position of spleen	*Assigned value*		*Per cent. of cases*	*Weighted value*
0	1	×	37	37
P	2	×	30	60
1	3	×	20	60
2	4	×	11	44
3 and 4	5	×	2	10
			100	into 211 = 2·1 average value

corresponding to position 1 of the average spleen

This computation fixes the position, not the mass or volume, of the average spleen.

[2] The position numbers refer to Fig. 31.

and at an age which assures a minimum of exposure to infection. Nevertheless, the amount of acute illness would be well worth knowing if we could only secure the information, for, as we have seen in Spain and in the United States, malaria of the hypo-endemic type, characterized by

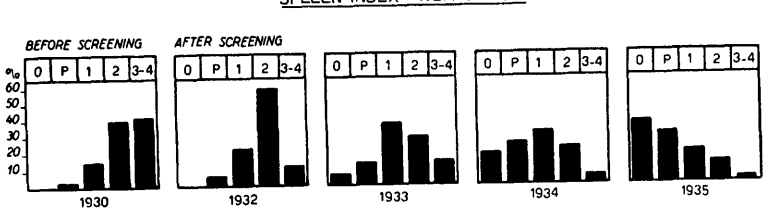


FIG. 32. GRAPHIC METHOD OF ANALYSING PROGRESSIVE CHANGES IN SPLEEN INDICES.

annual epidemics which leave few traces in the blood or spleen the following winter, may be of great economic importance. Dispensary records and a post-epidemic spleen and parasite survey are the best sources of information.

Attempts to combine all the different indices into one 'malaria index' are neither logical nor useful. Fever is malaria caught in the act, parasites show recent spread, and enlarged spleens constitute an historical record. The sum of them all would represent, of course, the proportion of the population showing any sign whatever of malaria, but what this figure would mean is hard to say. It is practically never used, because one might easily get the same index in two very different situations. It combines current events and history in such a way as often to conceal what the investigator wants most to know—not the amount of malaria, but the frequency of transmission and the strength of the defensive position of the population.

The relation between parasite index and spleen index is more valuable than any combination of the two. The malarious population is made up of acute cases in non-immunes with transitory enlargement of the spleen and persistent parasites; of chronic cases with persistent spleens

and transitory parasites, and of all gradations between. Theoretically this gives an explanation of the various parasite and spleen combinations, as follows:

Parasites without spleens: acute malaria in non-immunes, low intensity.

Parasite index greater than or equal to spleen index (*both high*): epidemic conditions—a recent wholly acute situation if the indices of children and adults are comparable; an acute exacerbation of an endemic situation if the child indices are greater.

Parasite index half of the spleen index: an endemic condition fading after a series of mild years, with lessening transmission.

Parasite index less than half the spleen index: low transmission now and recently, with bad years in the past.

Both indices low: sporadic cases, spaced infections, low intensity—hypo-endemic.

Spleen index over 50 per cent.: hyperendemic situation, or the remains of one.

The necessity for this complicated analysis arises from the principal defect of all the indices: as the intensity of infection increases, all reach a maximum at different levels and begin to decrease. In Africa a high inoculation rate may abolish almost all the signs of malaria in the adult. In the Belgian Congo only the infants have 100 per cent. spleen and parasite rates. But in addition to immunity there are so many factors to confuse the picture that the interpretation of malaria indices is not an exact science, but depends largely on experience and imagination.

Where no mosquito control is being attempted, malaria has a way of subsiding slowly over a succession of mild years, to be brought up suddenly by a bad season which puts things exactly where they were before. Those responsible for the health of a community do not commonly refuse to take the credit for the improvement, but they find an

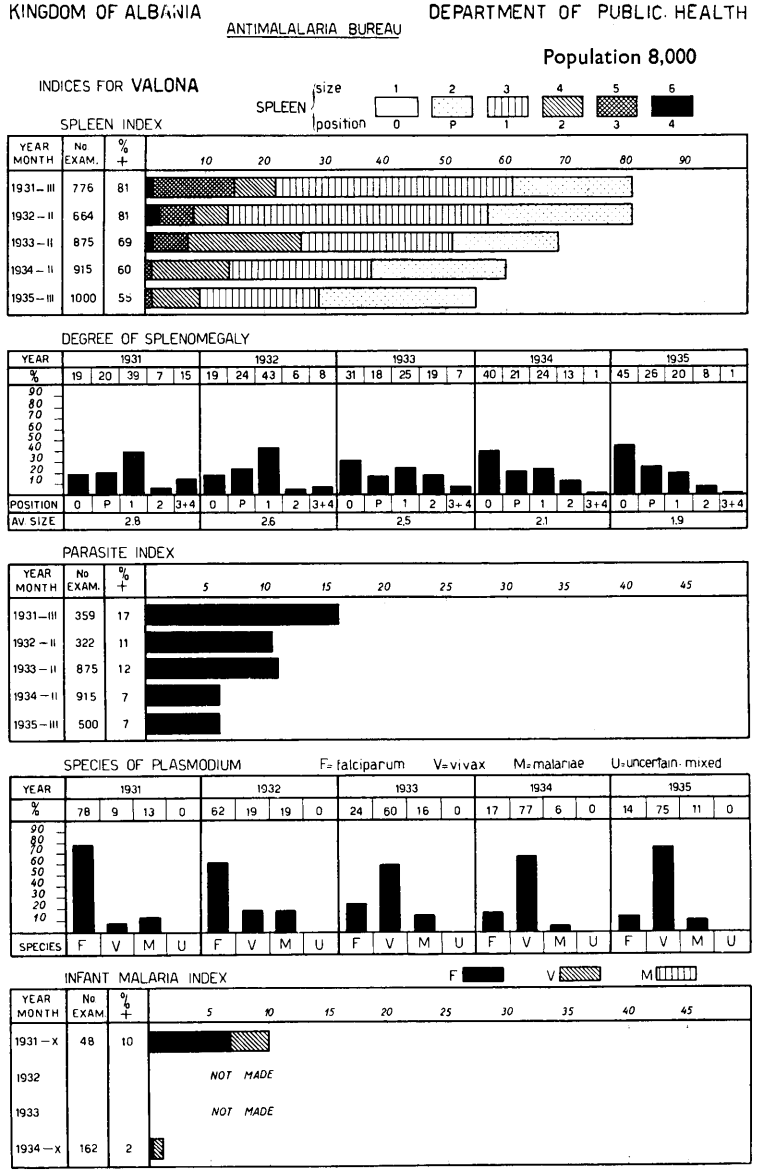


FIG. 33. CONVENIENT FORM FOR REPORTING OR DISPLAYING MALARIA INDICES OF A COMMUNITY OVER A FIVE-YEAR PERIOD

In this case the anopheles have been reduced but not exterminated in Valona. The effect on malaria is seen in the rearrangement of the spleen groups and in the predominance of *vivax* over *falciparum* infections, as well as in the quantitative reduction

excuse for the epidemic years by calling them acts of God. It was these five-, six-, or seven-year cycles of malaria which used to lend a transitory glamour of success to schemes of malaria control by drugs. One special method of quininization was reported to have reduced malaria in a certain village from 80 per cent. to less than 2 in the course of a few years, but strangely enough it seems no longer to be in use anywhere. The first epidemic year doubtless destroyed the public confidence in it. Such successes were very common not many years ago, and they remind us of the person who wrote to Trudeau for the latest specific against tuberculosis. Trudeau sent the patient a bottle with directions to 'take it quickly while it is still a cure'. But times have changed, and now, when we lay claim to success, we have to do more than impress the public or the civil authorities; we have to convince some biometrician, an unexcited person far from the scene of battle, who judges the results of our work in the clear cold light of the Theory of Probabilities and the Method of Least Squares. He wants to know what the likelihood is that the results are due to chance or to factors not under our control. For malaria has its natural ups and downs, linked with the highly variable climate of the temperate zone. A single year unfavourable to anophelines may reduce their density by 80 per cent., while a series of such years may almost put a stop to new infections. If we happen to dip our bucket into the sea of endemic malaria when the tide is on the ebb, we and the moon together can lower its level in a miraculous way; but if we set ourselves against it at the flow we are likely to suffer the humiliation of King Canute and emerge thoroughly wet.

One of the most important things we have to know in antimalaria work is whether malaria is going up or going down. If we start on the crest of a wave, we can count on a number of successful seasons with almost any method. If we start in the trough, we are set for an uphill climb.

Swellengrebel has reported in a rather amusing way an experiment in malaria control in some refugee villages in Bulgaria after the War. Antilarval measures were used in the villages south of Burgas and quinine treatment in those north. In 1927 quinine did not do very well and the antilarval measures were definitely more successful. But in 1928 the quinine results were wonderful, and it was almost decided to abandon larva control in favour of the easier way, when Swellengrebel[1] pointed out that there was an equal decline of malaria infection in villages where nothing was being done at all—in one instance from 32 to 9 per cent. in one year. We have to be continually checking up on nature to find out whether she is helping us or helping the anopheline mosquito. Our only protection from self-delusion and disappointment lies in keeping an eye on other places where the measures we are trying out are not being employed. These places serve as experimental 'controls'[2] against which to measure the value and significance of what we are doing. So individual are malaria problems that we are virtually compelled to set up a comparison area for every separate field of operations.

Comparison areas serve not only to reveal the trend of malaria but, what is equally important, to indicate the natural variations in anopheline density, on which the natural fluctuations in malaria depend. The observation of the local anophelines in a malarious locality is both a simple inspector's job of catching and counting, and a profound study for whole-time specialists. We rely on the inspector to check up on our antilarval measures; we look to the research laboratory to tell us how to adapt our plan of attack to the instincts and behaviour of the enemy. It is

[1] *L.o.N. Hlth. Org. C.H./Mal./*123, Geneva, 1928.

[2] The use of the word 'control' in English to mean both a check on the effectiveness of measures, and the measures themselves, leads to an ambiguity which we shall avoid by using the word only to refer to malaria abatement or prevention, and not to the use of special areas or groups for the sake of comparison or verification. Such areas will be called 'comparison areas' or 'groups'.

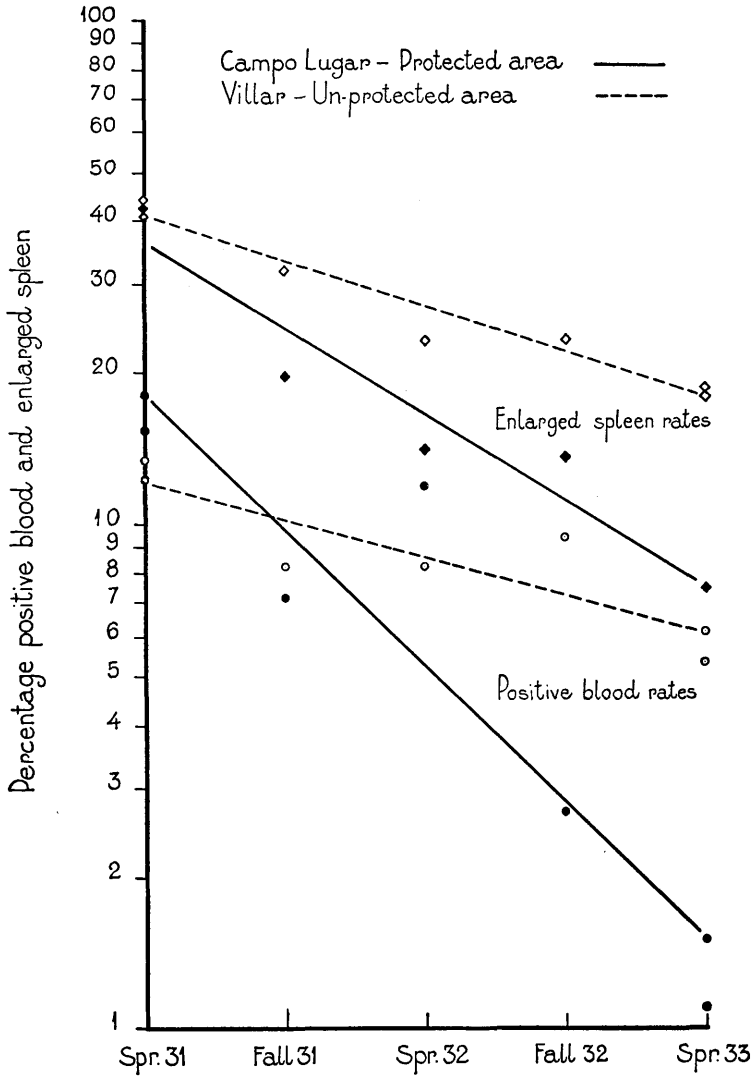


FIG. 34. GRAPHIC METHOD OF SHOWING THE TREND OF MALARIA IN A PROTECTED AND IN A COMPARISON AREA (Campo Lugar, Spain).

(*After* Hill. See also Howard, Earle, & Muench, *Suppl. Jl. Am. Statist. Assoc.* **30**: 249, Mar. 1935.)

surprising how often mosquito control is undertaken without going to the length of identifying the vector. But even when the vector is determined the problems connected with anopheline density are many and difficult. We desire to know what sort of catching station to choose and what numerical relation the anophelines we find in it bear to the total anopheline population. What is the proportion of the total number to those which bite man? Longevity of anophelines has an important bearing on malaria. The scarcity of infected anophelines in early summer may be due, as James once suggested, to heavy mortality during the season of sexual activity quite as much as to deviation by animals. What, then, is their average life-span in nature at different seasons? An increase in population reduces the *per capita* number of anophelines, but it also reduces the collective immunity. How far do these new-comers, babies or immigrants, help to divide the risk of infection and how far do they, as Christophers and Bentley said, heap 'fresh fuel on an already glowing fire'? Ross[1] and, after him, Lotka[2] and others have attempted to find mathematical solutions to the problems of malaria spread. The variables are so overwhelming that over-simplification of the problem often invalidates the results. For instance, Ross assumed that reinfections are the same as superinfections—that is, repetitions of the previous inoculation with the same organism—and therefore harmless and, for the biometrician, wasted. He assumed that the movements of anopheles were casual and non-purposive, like 'a cow grazing on a uniformly succulent meadow, or the random walk of an intoxicated person in a mist'. The difficulty is that the mosquito and the plasmodium do not seem to have any random habits. They do not behave like the black and white balls in the statistician's bag. They are like the little boy in Arkansas, who would 'ruther do what he'd ruther'.

[1] *The Prevention of Malaria* (London, 1910), ch. 5.
[2] *Am. Jl. Hyg.*, suppl. 3, Jan. 1923.

And furthermore, neither of them are the units Ross thought them, but instead collections of strains and races, so that the behaviour of one individual will often be quite different from that of another which looks exactly like it under the microscope. But the biometricians, besides establishing some essential rules of evidence, have told us one very important thing: that there is probably a critical *per capita* density of anopheline vectors below which malaria will tend to disappear altogether, instead of merely dropping to a lower level of intensity. A closer collaboration between biometrician and malariologist, and a better acquaintanceship of each with the methods of the other, is one of the most useful things we can work for to-day.

There is still another and much vaguer field of inquiry which traditionally forms a part of every malaria survey. We have referred to it very often in this book; we can only review it very briefly here. It has to do with social conditions among the people we are to protect from malarial infection. Certain of these are bound to influence our programme and enter into our prognosis. Is the population agricultural, pastoral, migratory? Has it stabled domestic animals? Are the houses screened? Are there many children? These are significant questions and we know why we are asking them; they have a direct bearing on malaria transmission. But when we put what almost every one believes to be the most important question of all—What is the economic condition of this population, how is it housed and fed, is it poor, crowded, or overworked?—then we are no longer on solid ground. We have cut loose from our experimental data and become engaged at once in a battle of opinion.

Few authors, in fact, have wasted much time in attempting to prove the decisive influence of economic depression on malaria; they consider it axiomatic. Boyd says: 'Surveys in some areas may result in the conviction that, for various reasons, malaria control by accepted methods is not

practicable; yet were the economic status of the affected classes improved, their condition would be greatly ameliorated and the disease no longer constitute a serious problem. Under these circumstances, malaria incidence looms larger as a sociological than as a sanitary problem.' Kligler asserts with even greater conviction that 'Malaria may be classed among the social diseases of a country. It is now recognized to be as a rule most prevalent and of greater severity in countries of low social and economic status. Its prevalence diminishes in proportion as the economic and social levels are raised. . . . Malaria like many of our social and community diseases may gradually disappear with the improvement of economic conditions, the more intensive settlement of the country and the intellectual development of the inhabitants. Progress of civilization is accompanied by the regression of malaria.' Ross, we might say in parenthesis, seems to have held the converse opinion. 'Malarial fever', he said, 'is important not only because of the misery which it inflicts on mankind, but because of the serious opposition which it has always given to the march of civilization in the tropics. It is therefore the principal and gigantic ally of barbarism. No wild deserts, no savage races, no geographic difficulties have proved so inimical to civilization as this disease.' Here the implication is not that barbarism maintains malaria, but that malaria maintains barbarism and should be directly attacked. Current feeling seems to hold, however, that malaria infection can be so interwoven with under-nutrition and low standards of living that the complex must be tackled as a whole, any independent solution of the malaria problem being out of the question. Colonel Gill[1] has expressed this idea clearly, if rather dogmatically, in his report on the malaria epidemic in Ceylon in 1934.

'The important part played by economic stress', he writes, 'in determining the local incidence of malaria, as determined by the spleen rate, is suggested by the fact that the spleen rate of communities is usually correlated (in the absence of a recent epidemic) with their economic status. . . . In the case of communities in which hyperendemic malaria is associated with economic stress, treatment by quinine or by other drugs is usually of little avail, and the same remark applies with reservations to anti-mosquito measures. In such cases, it is clear that, whatever other measures may be employed in economically depressed areas, they must be accompanied, if they are to be effective, by measures designed to promote rural betterment by increasing the food supply and by relieving economic stress. Finally, on somewhat similar grounds hygienic and sanitary schemes that are calculated to reduce the facilities for the spread of disease in general and of malaria in particular and to raise the powers of resistance of the population, must be regarded as anti-malaria measures of considerable importance.'

[1] Ceylon Govt.—Sessional Paper 23, Sept. 1935.

What is lacking to this case is any sound evidence, other than influential opinion, that it is true. The statement goes far beyond any proof that we possess. No one doubts that famine or other economic stress has an effect on malaria, particularly in its clinical manifestations, or that improvement in economic conditions may serve to mitigate it, but we have no example of any material diminution in malaria incidence brought about in such a non-specific way. Numbers of examples come to mind which show the contrary. In East Macedonia the most malarious region, the Plain of Chrysoupolis, is probably the most prosperous of the rural areas. A wet season produces a good crop, an inflow of money, and a high malaria intensity; but a dry year reduces malaria and prosperity at the same time. The spleen rate is much more apt to vary with the numbers of the anophelines than with economic status. In Calabria, as in Cyprus, all the villages are poor, but proper mosquito control has never failed to reduce spleen and parasite indices to insignificance in a short time. When, years ago, Dr. S. T. Darling visited an experimental area in Calabria he thought we should never make much headway against malaria there, so poverty-stricken was the

population. It was, however, one of the first to respond to relief from intense transmission.

The statement of Colonel Gill that treatment and anti-mosquito measures are usually of little avail to overcome hyperendemic malaria in the presence of economic stress is not supported by our experience. Only in a restricted sense, it seems to me, can malaria be considered a social disease, if by that we mean that the social and economic conditions of the mass of the population must be improved before any great decline in the endemic can be expected. It is true that war, disorder, and insecurity, that pioneering conditions and an undeveloped or unbalanced agriculture are conducive to a high transmission rate. But it would be a mistake to hold that malaria prevention through the reduction of transmission must wait upon the solution of the social problem. Malaria is a factor in ignorance and poverty, but the proposition is hardly tenable that ignorance and poverty must be greatly reduced before malaria can be made to disappear. Bentley once said to me in Calcutta that we must not be paralysed by the apparent impregnability of this triangle. Let us attack the side which is most vulnerable and we may be sure that we are at the same time striking at all three. This point of view is certainly upheld by health officers and malariologists of long and practical experience. General Hugh Cumming once said to a gathering of medical men in the southern United States: 'I think the statement is true that a seriously malaria-ridden population is incapable unaided of maintaining a well-balanced health programme. The obvious indication is to get rid of malaria first, put the community on a par with others which fortunately do not suffer from this handicap, and then proceed with normal development in affairs of health and of economic and cultural development.' And Sinton[1] is for attacking malaria to relieve

[1] *Rec. Mal. Surv. Ind.* **5** (3): 223, Sep., (4): 413, Dec. 1935, and 6 (1): 91, Mar. 1936.

economic stress: 'If India be at present in such a parlous state of over-population and deficient food supply and her people in such a state of chronic malnutrition as some economists believe, then there can be little doubt that it would be a paying proposition for India to take much more active measures to ameliorate the ravages of malaria if she cannot control them.' Malaria is an independent factor. As I once wrote with Missiroli, in an article on housing and malaria, the doctrine that social and economic uplift will ever obviate the necessity for laborious antilarval campaigns and the meticulous mosquito-proofing of houses does not seem to us well founded, either scientifically or in ordinary experience.

X

THE GENERAL STRATEGY OF MALARIA CONTROL

Too often the men in these positions have been long divorced from active participation in research. . . . They are out of touch with the fighting on the front line and their attention is too closely riveted to the maps and plans which lie on their tables. They fondly conceive that they have a clearer and broader grasp of what is going on than the captain in the thick of the fighting.

(PRES. JAMES B. CONANT of Harvard University. Address on Andrew Carnegie.)

SIR LEONARD ROGERS once said that the simplicity in theory of prophylaxis against malaria is only equalled by its difficulty in practice. This is principally due to the fact that the general strategy of the attack on malaria is subject to an adaptation to local circumstances and an opportunism beyond that required by any other major disease of mankind. As in war itself, each minor action requires a special and prolonged study of the terrain and of the forces and disposition of the enemy. Everything about malaria is so moulded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations. While this has provided a fascinating occupation to the epidemiologist, it has seemed discouraging enough to the health authorities. They have therefore allowed themselves too easily to be persuaded that malaria is inseparably allied to certain underlying social conditions which are amenable only to general hygienic measures such as housing, nutrition, and medical care, none of which are specially suggested by modern knowledge of malaria epidemiology. Labelling malaria a 'social disease' has, it seems to me, been the refuge of those who have come to despair of direct action.

The policy of subjecting malaria to economic sanctions

instead of launching a direct attack has received encouragement from the highest authorities. It is worth re-reading the Second General Report of the Malaria Commission of the League of Nations, published in 1927, to see how far we have advanced from the ideas and knowledge of a time so recent. The keynote of this report is the conviction that our knowledge of the mosquito transmission of malaria has not helped us in the struggle against the disease, and may in fact have led us away from the right path. The Commission at that time felt that we should, above all, strengthen the arm of the private and public physician with the frank aim of mitigating by medical assistance the lot of those who had fallen victims to a disease impregnable to frontal attack but bound eventually to succumb to an improvement in the social condition of the masses of malarious people everywhere. 'England, the Netherlands, and Denmark', continued the report, 'are examples of countries in which malaria was robbed of its importance as a cause of sickness and death without any knowledge of the epidemiology of the disease and without any reduction of anophelines having occurred.' There was hope, therefore, that malaria might in some unpredictable way disappear of its own accord from the Balkans, let us say, or from Africa and India.

An appeal to 'right living' as a substitute for measures based on a knowledge of disease savours somewhat of the philosophy of those cults which would lightly throw aside the fruits of diagnostic and therapeutic research to invoke the non-specific aid of natural powers of recovery, for which no skilful effort is required of either patient or practitioner. The natural powers of defence and recovery are there for us to call upon, but certainly we are not yet ready to discard the physician. Nature is not a faithful ally of man; she seems always to be quite as deeply interested in the success of the parasite and of the mosquito.

We have recently discovered that the principal difference

between the malaria of England, the Netherlands, and Denmark and that of southern Italy and the Balkans does not arise from differences in standards of living, but from the fact that the two regions have different anopheline vectors. The mistake was not in attributing the natural disappearance of malaria in the northern region to social changes. We do not yet know what was at the bottom of that disappearance, but, in view of the character of the special anopheline involved, it may well have been a certain evolution of agricultural methods in the direction of an increased animal husbandry. The mistake lay in holding up one region as an example to another without taking into account the differences in the epidemiology of the disease in the two areas. We cannot admit that any reasonable programme of malaria control can be recommended which is not based on a painstaking investigation of the local conditions underlying malaria transmission. Any subsequent resort to general measures of social uplift and hygienic betterment as a substitute for a specific attack on some link in the chain of malaria infection would be tantamount to a confession of ignorance or defeat.

Angelo Celli tells the story of the curious situation of some northern Italians who attempted to introduce Swiss cattle into southern Italy about the year 1898. At that time Smith and Kilborne had just discovered the method of transmission of cattle malaria through ticks, and so, although dipping was not practised, the cattle were kept in barns and never allowed to feed on natural pasture. They did very well, and it should be noted that it was not feed or care but protection against the tick which kept the cows healthy and made their owners rich. Unfortunately the owners were not acquainted with the mode of transmission of human malaria, and as a consequence all the herdsmen fell sick, many of them died, and the venture had to be abandoned. The men perished while the cattle remained sound. This parable teaches that the discovery of Ross and Grassi should certainly in the course of time produce economic and hygienic results far greater than even those brilliant applications which followed the work of Smith and Kilborne.

Schemes of malaria control, then, should be based on knowledge and not on faith. But the health officer cannot possibly acquire this knowledge single-handed. He must have at his back a malariologist with a research laboratory equipped to carry out every kind of field study. A malariologist nowadays has to be something of an entomologist, protozoologist, and experimental biologist as well as a doctor of medicine.[1] He is, in fact, a medical parasitologist who has specialized in a disease instead of in a parasite. There are several brilliant exceptions to prove that a medical training is not obligatory, but it is of inestimable advantage in dealing with sick people, even *en masse*, and with the medical and civil authorities. It makes the malariologist the health officer's chief instead of his assistant. The malariologist himself should be able to call on expert assistance in the numerous fields which touch his own on all sides. Thus his field stations will be supported by the more diversified laboratories at the centre. But if these do not exist, he will demand at least an entomologist for his staff.

The health officer must always have at his right hand a drainage engineer. 'Any scheme', as Russell says, 'more complicated than a simple short ditch requires technical knowledge not possessed by the average health officer.' Furthermore, a doctor should have a competent engineer as his ally in the inevitable conflicts with other engineers. In many well-populated and highly cultivated areas it is not an exaggeration to say that most of the places where mosquitoes breed are the result of man's interference with natural drainage. All the malaria of the Ganges delta, according to Bentley,[2] is of this kind, and R. C. Connor[3] of

[1] Swellengrebel, N. H., *Suppl. Riv. Malariol.* **14**, sec. 2 (3): 73, 1935.
[2] *Malaria and Agriculture in Bengal* (Govt. Press, Calcutta, 1925).
[3] *Milit. Surgeon*, **77** (1): 4, July 1935.

the United Fruit Company says that on the Cuban plantations 75 per cent. of the anopheline breeding-places are man-made. 'For the most part', he adds, 'man-made foci of mosquito breeding can be attributed to the negligence and carelessness of construction engineers. After insanitary conditions have been created by them it is usually a difficult problem to get them to spend the money necessary to correct them.' And Le Prince,[1] himself an engineer, says of Panama, 'It is surprising how many mosquitoes are unnecessarily brought into existence by people who are aware that the construction work they are doing will cause *Anopheles* to multiply. They do this when it would cost no more to arrange for proper drainage. . . . Such conditions have been created by engineers who knew the ensuing results, but were apparently in no way interested provided they did not suffer personally or financially.' Until construction engineers develop a conscience with regard to malaria, they must be regarded by the health officer as one of the most dangerous and difficult of his malaria hazards. 'Engineering', says Sir Malcolm Watson, 'which leaves a trail of malaria behind it, is bad engineering.'

The health officer and the public works engineer are, so to speak, natural enemies. Each is busily engaged in activities which tend to increase the cost of the other's work and is too often an ignoramus in the other's special field. All that is needed to effect a fruitful collaboration is an intelligent and well-informed higher authority. The danger arises when the civil authorities do not seek competent advice. It is astonishing how often they will cheerfully embark on some important and costly enterprise without taking into account the technical knowledge at their disposal. After the War, for example, masses of people had to be moved from one country to another in the Near East. It was usually necessary to locate them in the most malarious regions since that was where there was the most room. In Greece alone,

[1] *Mosquito Control in Panama* (New York & London, 1916).

1,400 new villages were constructed to house over a million refugees, and similar provision had to be made for the populations migrating to Bulgaria, Yugoslavia, and Albania. The preparations were carried out under the auspices of the League of Nations, and funds were largely obtained from international sources, yet it would appear from the results that it was not thought necessary to call upon the aid of specialists in malaria, or for that matter of hygienists or sanitary engineers. Houses were built in most villages in such a manner that it was afterwards found impossible to make them mosquito-proof, although this would have added less than 10 per cent. to the cost of each house. The fact that usually no provision was made for water-supply or latrines is a detail.

The most discouraging situation of all arises when governments have actually set up a competent organization for malaria studies and surveys, and then neglect to consult it or make a practice of disregarding its advice. It happens more often than we should suppose. 'Advances', writes Sinton,[1] 'have been hampered not only by active opposition due to ignorance of the serious handicaps imposed by malaria and the ease with which they can be profitably overcome, but . . . even by deliberate apathy and wilful neglect of expert advice although the expenditure could be afforded.' Whatever the reasons may be for this—bureaucracy, ignorance, or false economy—the world is strewn with the unfortunate results. Magnificent irrigation projects designed to fertilize great unproductive areas end by needlessly waterlogging the soil and infecting the population. We need not look far in any malarious region to find absurdly planned and badly carried out colonization and land reclamation schemes, which fail for lack of knowledge of malaria properly applied. Paul Russell has recently unearthed in the Philippines an entomological report, written and carefully filed in 1904, noting that the only

[1] *Rec. Mal. Surv. Ind.* **6** (1): 91, Mar. 1936.

infected mosquitoes were stream breeders. Here was the key to the mystery of Philippine malaria, but for twenty years thereafter the 'official' source of malaria remained unshakably the classical one of stagnant water in ponds, marshes, and swamps, as it was 'at home'.

Of all the reasons for not setting up a malaria research body, the financial one is probably the worst. Malaria is an expensive disease. The direct cost of the Ceylon epidemic was £350,000, but endemic malaria can be an even greater economic burden, as Sinton has recently pointed out in his analysis of the situation in India. There is a record that 90 miles of railroad in India cost a million pounds over estimate on account of malaria. It is very costly to ignore it; it is even more costly to attack it in an ignorant way. When we think of the thick fog in which both treatment and prevention of malaria were carried on only a few years ago, we cannot wonder at the general confusion and discouragement of that time. As soon as attention was directed to the anophelines as the only transmitters of malaria the entomologists began to find new species everywhere, with the most diverse habits which permitted them to breed in all kinds of water and constitute a universal menace to mankind. The world suddenly seemed crowded with anophelines and the task of getting rid of them almost superhuman. Stephens and Christophers[1] in India began the careful work of separating the dangerous species from the less dangerous and from the quite harmless. This led to extraordinary discoveries. Widespread and prolific insects such as *Anopheles rossii* were exonerated completely, while unsuspected species present in small numbers were found heavily infected. The investigation of a curious little problem of the convict settlement in the Andaman Islands unexpectedly revealed a scarcely known mosquito, found breeding in salt water, as the chief vector of the whole Dutch East Indian archipelago

[1] *Suppl. Riv. Malariol.* **14**, sec. 2 (3): 87, 1935.

as far as the Celebes. Similar surveys, wherever they have been made, have clarified and simplified the malaria picture, although there are still wide areas (as, for example, in Australia and in China) where the identity of the principal vector is not yet known. A baker's dozen of anophelines carry most of the malaria of the world. With the field constantly narrowing, attention has been focused on the true culprits. Studies of their habits and adaptations permit a further sharpening of the attack, and malariologists and engineers in combination have developed methods with a specific aim and tested value which can save a tremendous amount of money to the state and the individual.

It is evident why these studies cannot be carried out in a few great central laboratories in the world for the benefit of all. Selected and uniform methods of survey and experiment can be tried everywhere, but their fruits will not stand transplanting, even for short distances. It is known, for example, that the two vectors of malaria for all Central and South Africa are *A. funestus* and *A. gambiae*. The latter breeds in every kind of standing water, particularly in marshes. In the Union of South Africa this appeared to be the great obstacle to malaria control, because of the expense of draining or filling the marshes. However, Swellengrebel[1] discovered that the *gambiae* of the Union of South Africa is not the same as that of the rest of Africa. It chooses for its breeding-places only the little temporary rain-water pools open to the sun and without vegetation. This biological difference, which does not correspond to any morphological difference at all, changes the method of control completely. Watson found that the clearing of jungle which did away with *A. umbrosus* in coastal Malaya would greatly increase the malaria a few miles inland by rendering streams attractive to *A. maculatus*. Thus the best method in one place may be the worst possible thing to do only forty miles away. On the western coast of Italy the marshes at Naples

[1] *Pubn. S. Afr. Inst. Med. Res.* **4** (27): 245, July 1931.

and those at Pisa may be neglected entirely as far as the public health is concerned, though they produce anophelines in prodigious numbers. But the marshes in between, on the coastal plains of Rome and of Grosseto, have required the expenditure of millions of lire on malaria control. Clearly governments can trust to no formulas devised in Geneva or elsewhere, but must create the simple machinery necessary to define and resolve their own problems, locality by locality.

That this is profitable can be inferred from the adequate antimalaria organizations of large commercial and agricultural enterprises in the tropics and elsewhere. The Medical Department of the United Fruit Company, writes Connor, is responsible for the health of 150,000 people, and most of the illness and loss of labour days is due to malaria. Every one in the Company knows that malaria control increases individual earning power, but only if there is confidence and co-operation from manager to humblest labourer. 'The change of an overseer in Cuba usually influences the malaria rate, up or down.' How sensitive is management to influences which affect the earning power of labour! 'The support of the executives in Boston', Connor remarks, 'is secured, and all managers of tropical divisions are instructed to co-operate in the sanitary programme.'

This is the sort of backing the health officer needs and so often fails to get. The apathy of governments to the devastating effect of malaria on the population is in part due, Connor believes, to the insidious nature of the disease, which does not, like yellow fever, create demoralization and panic. People become habituated to endemic malaria, it is true. But in my experience the inaction of governments in the field of prevention is due rather to a profound scepticism induced by lack of permanent results from previous expenditures on malaria control. This pessimism often extends even to the medical advisers of governments and to local medical officers, who, like the army men, have usually been

trained in clinics instead of in schools of hygiene. In the early years, as Watson says, malaria control fell to clinicians like himself, most of whom were unable, as he did, to change their point of view. The result was that medical assistance absorbed the major portion of the health budget, leaving little for the prosecution of field studies and the application of larva control measures. Even now, governments tend to feel a greater obligation toward the sick than toward the well. Martini once remarked that there seems to be more joy over one case redeemed from malaria than over the ninety and nine who do not get infected. The health officer must take the other stand. The treatment of clinical malaria with any of the drugs at our command is not yet a preventive measure capable of reducing the amount of transmission by mosquitoes. It is not the health officer's duty to treat malaria fever or to pay for such medical assistance out of his budget. On the contrary, enough money could often be spared from a treatment budget unable to produce any lasting effect, to carry on a considerable programme of preventive measures. It is, of course, an absolute anomaly to organize a medical service, as was done in some of the refugee villages in the Balkans, for the sole treatment of malaria in a population completely deprived of all other medical care.

But if the health officer succeeds, as he must, in securing the support and confidence of his 'executives' in a well-considered programme for reducing malaria transmission, he can never hope to get the same co-operation from the 'humble labourer' which his colleagues on a great plantation secure in one way or another. Theorists in malaria control may classify methods as direct and indirect, primary and secondary, general and specific, and what not, but to a health officer with experience antimalaria measures fall naturally into two groups: those in which he has to persuade the people to participate, and those independent of their goodwill or assistance. The 'direct' attack on the

parasite by treatment of infected persons and the daily killing of anophelines in houses is preferred in the Second Report of the Malaria Commission to the 'indirect' measures of mosquito control through drainage or larvicides. But there is no way of compelling villagers to take plasmoquine or to catch mosquitoes. In either case a few recalcitrants may render the whole campaign ineffective. This does not depend on the intelligence of the people. In Macedonia in 1916 Sergent found, by making surprise examinations of the urine, that not only the French soldiers but also the officers were avoiding when possible the daily ration of prophylactic quinine. In Holland the farmers moving on to the new land reclaimed from the Zuider Zee—the famous Wieringermeer polder—became frightened by a few cases of malaria and proceeded with insecticide sprays to exterminate all the anophelines they could find in their houses. This unusual activity continued, according to Swellengrebel, only as long as the population remained afraid and the insecticide was furnished free of charge. The killing of anophelines is not natural to peasants, who will tolerate almost any number, and the efforts soon relaxed. Threatened with an unfamiliar danger people react energetically and sometimes go to ridiculous extremes, but they become habituated to it all too easily. 'Les malariens', states Marchoux sadly, 'manifestent fréquemment une grande indifférence à leurs misères.'[1]

But if the victims themselves are indifferent, their natural powers of recovery, over which they have no control, are co-operating effectively all the time with the health officer. The buoyant responsiveness of the community health to any lessening of the usual intensity of malaria, by which we mean frequency of inoculation, is the most surprising and heartening thing about malaria control. The final aim is, of course, to bring the transmission rate below that critical level at which new infections keep pace with recoveries, and

[1] Malarious people often show a great indifference to their miseries.

it is often stated that until this is achieved there can be little change in the malaria situation. But this is to take account only of the *amount* of malaria, not of its *intensity*. When anophelines are present in such numbers that they succeed during the summer in infecting virtually every one in the community, then the incidence of malaria can go no higher. But this does not mean that anophelines can do no further damage. This is the point at which hyperendemicity begins. There seems to be no saturation point for malaria in the temperate zone. Even to a person already infected with malaria new infections bring serious consequences. Inoculation with a different species or a different strain of plasmodium is like contracting a new disease. It gives rise to symptoms, postpones recovery, throws a new burden on the spleen, and puts gametocytes into circulation again. Any reduction in anopheline density begins by removing layer after layer of these superimposed infections before it cuts down the amount of malaria, or number of infected persons. A hyperendemic condition must first return to ordinary endemicity before it changes to epidemic malaria and eventually becomes reduced to sporadic cases under the influence of a constantly diminishing transmission rate. If the situation is not hyperendemic to start with, any decrease in anophelines will be immediately reflected in the incidence of the disease, which will recede until it comes into equilibrium at a lower level. And if the anophelines can be brought below a certain 'critical' density, malaria, as Ross showed, will go on decreasing at an accelerating rate until it is entirely gone.

The complicated mechanism of malaria transmission renders it naturally uncertain and open to attack, so that the odds are always against its successful fulfilment. For every transfer accomplished in nature there are innumerable failures. A persistent campaign of obstruction, in my experience, tends to have a cumulative effect. The same measures produce greater results the second year than the

first, and the third year than the second. This crescendo of effectiveness depends on well-known factors which come into play as transmission declines, and work independently in our favour, setting up a 'beneficent cycle', which may be defined as one resisting changes for the worse. This was suggested by Edmond Sergent at the First International Congress on Malaria when he said: 'On constate qu'heureusement le danger de contamination décroît plus vite que ne diminuent le nombre des porteurs de germes et celui des vecteurs de germes.'[1] This is due to the fact that the number of carriers and the number of vectors are not unrelated variables but the one depends on the other, so that, if the vectors decrease, the chances that they will meet carriers go down even more rapidly. The results of protecting human beings from the bites of anophelines, either by mechanical means or by increasing the number of sheltered animals, have also a disproportionate influence on malaria transmission. If the chances are already small that a mosquito will succeed in biting a man, the odds against its biting two men at different times are not doubled but squared. Thus, as in some malarious districts of Spain, if 1 in 20 *atroparvus* is found on the average with human blood then only 1 in 400 will probably make a second contact, so that, if the proportion which bite man could be cut in half, the odds against repeating would increase four times. This gives us the long end of the lever in the fight against the mosquito, especially in dealing with anophelines like *maculipennis* which willingly bite animals. This would be most evident in situations of mild endemicity, as in Spain, where in fact a recent experiment in larva control carried out by Hill at Campo Lugar brought about a more rapid reduction in malaria than in anopheline density. This should not have been unexpected. The same thing occurs everywhere, disguised by hyperendemicity or by a general

[1] It appears that the danger of infection decreases more rapidly than the number of carriers or the number of vectors.

loss of immunity which aggravates the severity of new infections.

The whole edifice of malaria is supported on a certain critical frequency of new infections. That is why the health officer visualizes malaria not in terms of fever-stricken individuals but of infected mosquitoes. His aim is to reduce their number, and this is rarely such a fantastic undertaking as many who speak with authority on malaria would have us believe. A defeatist attitude with regard to mosquito control is usually based on theoretical considerations and not on practical experience, for of all the field directors of many nationalities and temperaments whom I have employed or observed, I do not recall a single one who failed to convince himself of the soundness of the method. And with reason, for in the whole Mediterranean basin, from Spain to Palestine, I know of no competently planned project for malaria control by antimosquito measures which has failed to accomplish its object at reasonable cost, even under very difficult conditions.

Consider the logical evolution of antimalaria work in Albania, a hyperendemic region, with a population in the main poor and primitive in habits and mentality. A central malaria organization called the Malaria Bureau was set up in the Health Department, which at the time was occupied entirely with the problems of general medical assistance. The Bureau consisted at first of a malariologist and a drainage engineer, both on loan from abroad, and an Albanian field director. It proceeded to gain experience and the attention of the government by cleaning up the principal port, Durazzo, a miserable little town situated beside an enormous sea-level marsh some 20 square kilometres in area, breeding innumerable hordes of *Anopheles elutus*. An entomologist was added to the staff and given a laboratory, to study the rather complicated situation with regard to the local varieties of *maculipennis*. By an ingenious scheme of salinification, founded on observational data supplied by the entomologist,

malaria transmission was completely stopped within three years in Durazzo, so that the town became a sea-side health resort and began to grow amazingly. Other towns immediately demanded similar attention, and for a time one new field-station was created each year to handle these requests. The towns themselves set aside funds in their annual budgets to maintain these stations permanently. Now the local malaria stations are being transformed into health centres with general programmes of health protection, and at the same time the field directors by winter training and grants for study are being turned into health officers. As Strode says, 'We do not necessarily need a fully developed health system before attacking special problems; we often begin by attacking certain diseases in order to develop a general system.'

Such a central malaria organization supports a continued and consistent policy of malaria control; it makes surveys of communities, draws up programmes and carries them out; prevents the interest of government from slackening, and constantly uses the material at hand for field studies and research impossible to laboratories in London or Berlin. It gradually earns the confidence and backing of the authorities and of influential citizens throughout the country. It will need this as the local immunity evaporates and hostile physicians create epidemics out of sporadic cases of acute malaria which make more impression than the memory of a thousand chronic cases which have disappeared. I remember at Portotorres, in Sardinia, after three or four years of successful interference with transmission, the Mayor actually believed that the malaria was getting worse because of the increasingly acute course of the infections which still occurred. The methodical collection of spleen and parasite indices and the intelligent handling of comparison areas will begin to command attention across provincial and national frontiers. Well-documented results impress organizations like the Malaria Commission of the League of Nations,

whose duty it is to evaluate and make public advances in malariology. And the spreading influence and prestige of good work will eventually reach even those cold heights where, out of touch with the fighting in the first line and long divorced from active participation in field work, the High Command often exerts a determining influence on the strategy of the battle.

XI

FUNDAMENTAL LINES OF ATTACK

Perfection and speed in any line of human endeavour are expensive. There must rather be constant striving for continuity of modest effort.

P. F. RUSSELL

ALMOST everything that can be done to make malaria infection less frequent falls rather naturally under five heads:

Suppression of gametocytes in human carriers,
Protection of human beings from mosquitoes,
Destruction of larvae in the water,
Permanent elimination of breeding-places,
Natural methods of control.

There is no objection at all to using any combination of these methods which seems expedient, and within one's means. In fact they are hardly ever employed individually except in experiments. Celli wrote at the end of his book on malaria in large capitals:

UNUM FACERE, ALTERUM NON OMITTERE

The objectionable thing is the shotgun method of applying them indiscriminately without knowing how far the cost of each is justified by results under local conditions. It is not rare to find inexperienced people attempting everything badly and accomplishing nothing, a plain example of what Coleridge called 'nimiety'. This is doubtless what the Malaria Commission was referring to when it advised against using all the available measures at once. No method of control is economical which costs more than it is worth, or which is unnecessary to secure the desired end. But there is no *a priori* reason why simultaneous attacks on different fronts should not be better than a single offensive. Cromwell's order was: 'Neglect no means.'

1. *Treatment as a Preventive Measure*

By the year 1900 Robert Koch had evolved a method of intensive treatment with quinine which if rigorously applied to whole communities would, he felt sure, solve the malaria problem everywhere. 'After all these experiences', he wrote, 'I consider myself warranted in stating that we are in a position, by means of the procedure which I have described, to make every malarious region according to circumstances wholly or nearly free from malaria.'[1] While the experience of the last thirty-five years has somewhat attenuated the optimism of this declaration, the feeling is still strong that treatment is a powerful weapon of prevention in the hands of the malariologist. It is not unanimous, for Swellengrebel put himself on record years ago as follows: 'In my opinion treatment belongs to medical assistance whereas the anti-mosquito activities belong to public health, but I know that I differ there from the opinions expressed in the Second Report' [of the Malaria Commission]. Nocht, however, at the Geneva meeting of 1928 said, 'The treatment of malarious individuals is essential to all antimalaria campaigns'; and the Malaria Commission[2] in 1934, after admitting the value of antilarval work in Palestine, continued: 'It should be added that the success of the antimalaria work is equally due to treatment of the cases.'

In 1927 we established a laboratory in the little Sardinian town of Torpè, which has about a thousand inhabitants. Employing a doctor and a nurse we attempted and virtually succeeded in treating every attack of malaria or parasitic relapse as soon as it could be detected, and we continued this intensive therapeutic campaign for three years. The supply of quinine was unlimited and it was pressed upon the patients in quantities which were unnecessarily large. In fact, the average consumption per case treated was well over 25 grammes, two and a half times the amount we should

[1] Translated by R. Ross in *The Prevention of Malaria* (London, 1910), p. 38.
[2] *L.o.N. Hlth. Org. C.H./Mal./212*, Geneva, 1 Mar. 1934.

now consider ample. The table shows that the incidence of malaria actually increased every year, for while the growing number of treatments might have been due to the increasingly co-operative relationship between the nurse and the people, the spleen and parasite indices leave no room for doubt.

Effect of Intense Quininization at Torpè, Sardinia

	Individuals treated	*Quinine given*		*Spring indices*	
		Total grammes	*Per capita grammes*	*Spleen*	*Parasite*
				%	%
1926	..	..	..	75	22
1927	644	24,400	38	85	25
1928	868	23,500	27	94	13
1929	915	26,700	29	92	36

The quinine did a great deal of good. It could not reduce the amount of malaria but it repaired the damage caused by the parasite, it diminished the spleen volume, and lowered the death rate. The children in particular gained in weight and in physical well-being. 'Many doctors', writes Missiroli, 'observing the reduction in damage to the human organism in a population well treated with quinine, continue to confuse treatment with prevention which aims at the suppression of the causes of the endemic.' Doubtless Koch and so many others after him misinterpreted this obvious improvement in the health of the population. Certainly at Torpè there was no evidence of the suppression of the causes of the endemic.

However, the majority of the leading European malariologists,[1] while often admitting that quinine is not of much value in preventing the spread of malaria where it is hyperendemic, still contend that in northern countries, where the anopheline is not an insistent man-biter and the plasmodium is mainly *vivax*, the mild endemic malaria which once prevailed has disappeared from the relatively well-to-do popu-

[1] Cf. articles and statements by James, Brumpt, Marchoux, Nocht, Mühlens, and many others.

lations mainly because the people sought and obtained proper treatment. There are two good reasons for doubting this. Malaria shows no tendency to disappear from certain districts of northern Holland and Germany, where the people are on the whole as well-to-do and the physicians as competent as in the adjacent areas, and in Spain a vigorous attempt over many years to root out malaria by treatment has not succeeded, although the vector is the same as that of England, France, and Denmark, and the infection rate is so low that it barely keeps pace with the recovery rate. In many places in Spain, as in the United States, the average person runs little risk of being infected oftener than once in two or three years, and hence there is little accumulation of malaria. Parasites and enlarged spleens are difficult to find in the winter. The village of Majadas with 700 people had 100 cases of malaria in 1929, but the spleen index and the parasite index were both 1 per cent. in the following spring. In March 1930 I visited a rural school at Corchuela with 100 children, 47 of whom had had acute malaria in 1929, but with the utmost patience and care I was able to palpate only 3 spleens. The spleen index goes up and down with confusing rapidity, for these are the acute spleens of Christophers, undependable as a measure of immune reaction. It is precisely in such situations that treatment should give the best results, and treatment has for centuries been the method of choice in Spain. Dr. José Masdevall,[1] physician to King Charles III, wrote to His Majesty from Seville in 1787: 'Puisque la quinine est si efficace pour guérir et prévenir ces malades, je ne puis que supplier Sa Majesté de bien vouloir prendre les mesures les plus appropriées pour que toutes les villes de ce continent soient pourvues d'un antidote si énergique, et pour qu'il soit vendu à un prix modéré.' A hundred and fifty years later we still read in an official statement[2] that

[1] Cited by Pittaluga, *L.o.N. Hlth.Org. C.H./Mal./*26, 30 Sept. 1924.
[2] Edit., *Med. Pa. Cálid.* **4** (2): 127, March 1931.

'the basis of antimalaria work in Spain is supervised treatment of the sick'. Quinine in fact appears here at its very best. One sees all the general advantages arising out of well-organized medical assistance—healthy-looking children, a lowered death rate, and the absence of *falciparum*. The trouble is, malaria does not disappear. In Talayuela, for example, one of the towns receiving special attention for many years, 12 per cent. of the population had malaria in 1921, and 11 per cent. in 1929. In prosperous districts, where quinine has been taken in abundance for years, no improvement in organization or technique, writes Sadi de Buen,[1] seems to have any effect on incidence. 'It seems', he adds, 'that with quinine one can obtain results up to a certain limit which cannot be surpassed.'

We now have a synthetic drug, plasmoquine, that will kill gametocytes in the blood in doses which are well tolerated. We decided to shift from quinine to plasmoquine in Torpè, the little town which I have described above. During 1931, the first year of our new experiment, we thought it would be sufficient to treat cases as they arose. Two nurses went about examining and treating the slightest indispositions on the theory that individuals usually became carriers after some acute manifestation of the infection. The effect, however, on the endemicity and on the anopheline infection index was absolutely nil. People became carriers without symptoms or had already infected mosquitoes before we could get to them.

It would be very useful to be able to identify the individuals who constitute the reservoir of infection in a community, and who are probably not very numerous at any one time. The text-books give a simple representation of the transmission of malaria as three links of a chain, framing the pictures of two human beings with an anopheles mosquito between them. One is a haggard anaemic individual, evidently representing the source of infection, and the other

[1] *L.o.N. Hlth. Org. C.H./Mal./*125, Geneva, Jan. 1929.

a happy, florid, unsuspecting person destined to become the next victim. Nothing is easier than to tell them apart in the picture, but in nature the gametocyte carrier is one of the most elusive individuals one can imagine. Healthy-looking young people turn out to be swarming with parasites, while chronic old cases show none at all for months on end. There are no outward signs to mark a carrier and no symptoms by which he can appreciate his own condition. We only know that the more malarious a person appears, the less likely he is to be a source of infection to others.

It would be worth while going to a good deal of expense and trouble to find the carriers by a general examination of the population, as we do sometimes in typhoid fever, if their condition were less transitory. Gametocytes come in waves into the circulating blood, appearing and disappearing like the other parasites without apparent reason. Harmless to-day, a person may become a dangerous focus of malaria to-morrow without knowing anything about it. To reach this small but shifting group of infective individuals, it is far easier and less expensive to treat everybody from new-born baby to oldest inhabitant at regular intervals than to make frequent blood examinations of the whole population. Certainly the younger age-groups are more dangerous than the older, since they are always relapsing, but it would be a mistake to limit the examinations or the preventive treatment to babies and children. Adults, too, become carriers off and on, and the havoc they work is out of all proportion to their numbers. We have only to think of the town of Nemi, considered non-malarious for centuries by all ordinary standards, to which the creating of an anopheline breeding-place brought an epidemic of malaria involving two-thirds of the population. Single individuals, who by some perverse destiny become splendid and persistent infectors of mosquitoes, may affect the malaria intensity of an entire village. 'It is our opinion', write Barber and Komp,

'based on a considerable experience in blood parasite surveys, in the testing of gametocyte carriers by mosquito infection experiments, and in the dissection of anopheles caught in dwellings, that it is the occasional heavy carrier who is most dangerous to a community.' Clark thinks the fatal disposition runs in families. But, at any rate, no one has ever succeeded in rounding up all the carriers and making them sterile. A multitude of anopheles searching everywhere between sunset and sunrise make contacts with all the human distributors of infection, but a few doctors sampling here and there with their needles fail more often than they succeed. 'Reservoirs' of malaria infection hardly exist; there are only hidden springs breaking out in unexpected places and drying up as fast as they are found. This is why the carriers in a malarious population cannot be identified and registered, much less isolated or sterilized as we sometimes attempt to do in other diseases.

In 1932 we abandoned any attempt to pick the carriers and treated the whole population with plasmoquine on alternate days during June and July, the only period when we thought the anophelines numerous enough to be dangerous. To be on the safe side we continued to treat children under twelve until the end of August, knowing that they are always the principal sources of infection. The result was a partial success, for we actually postponed the annual wave of new infections for two months. But the treatment of the children alone accomplished very little. The occasional heavy carrier among the adults nullified our efforts completely, even though we were unable to detect him. We are therefore sceptical of the Malaria Commission's theory[1] that 'results of this kind [rarity of gametocytes in adults] show how important it is before beginning an attempt to reduce malaria in a locality by a system of gametocyte therapy, to ascertain precisely at what age-periods of the population these forms of the parasite are most prevalent and to concentrate our efforts on persons within these age-periods.' With a dense anopheline population of dangerous vectors, all age-groups furnish carriers.

[1] 'Therapeutics of Malaria', *Quart. Bull. Hlth. Org. L.o.N.* **2** (2): 181, June 1933.

In 1933 we determined on a large-scale experiment in the near-by town of Posada with the somewhat smaller population of 771. Here everybody without exception was given plasmoquine treatment for the entire malaria season from 15 May to 21 October. It was difficult to treat the babies less than a year old, and we succeeded with only about half of them, but only 46 individuals failed to take the treatment throughout the entire period. The resulting diminution of malaria as compared with the contrast group and with the same village in a previous year is striking (see Figs. 29 and 30, pp. 219 and 220). Not a single infected anopheline was found in the experimental village as compared with 2 per cent. of those caught outside. An unexpected result was that *P. vivax* was virtually eliminated from the treated population.

The discouraging feature of the experiment was the large *per capita* expenditure in five months of 29·40 lire, which is about 6*s.* 6*d.* Unlike the cost of larva control, this goes up with the population. We were engaged at the time in carrying out larva control measures in the adjoining town of Siniscola, and providing satisfactory protection for a population of 5,000 at an annual cost of 18,000 lire. Had we attempted this with plasmoquine, it would probably have cost eight times as much (Fig. 35). This seems to be the general experience. Wallace[1] has used plasmoquine on rubber estates in Malaya and reports a monthly cost of one Straits dollar per person, which is even more than that at Posada. Russell came to the conclusion in the Philippines that the 'cost of one adequate drug control experiment would

[1] *Malayan Med. Jl.* **8** (3): 145, Sep. 1933.

be more than the cost of Paris greening for several years'. It is quite likely that some time we may have an equally effective but much cheaper drug than plasmoquine. In that case I believe that if it could be combined with quinine, or given to every convalescent case of malaria for a month or so, the

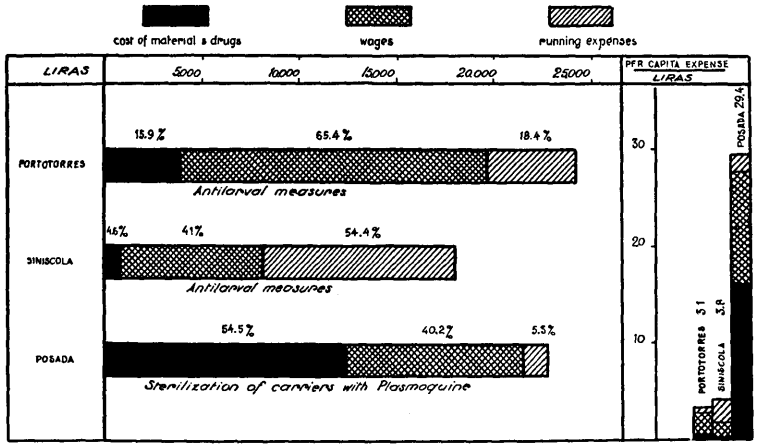


FIG. 35. PER CAPITA COST OF LARVA CONTROL COMPARED WITH THAT OF STERILIZATION OF CARRIERS WITH PLASMOQUINE.

effect on the transmission rate would be significant. It is practically impossible, however, as Kligler found in Palestine, to keep a population gametocyte-free, at any cost. It is not likely that any form of mass treatment will ever prove a satisfactory substitute for mosquito control where that is feasible.

2. *Protection from Anophelines*

The custom of screening or mosquito-proofing houses in America began in the late seventies or early eighties of the last century. Many millions of dollars are now spent annually for this purpose, and the separation of anophelines from human carriers must have influenced the course of malaria in the United States. The fact that houses are

FIG. 36. TYPE OF WINDOWLESS HUT WHICH USED TO PREVAIL IN THE PONTINE MARSHES WHEN THE REGION WAS EXTREMELY MALARIOUS
All the inhabitants fled to the mountains in summer

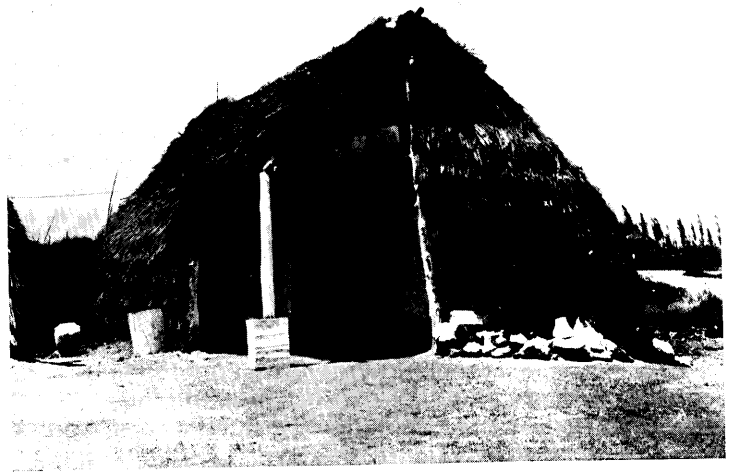


FIG. 37. TYPE OF WINDOWLESS HUT ON THE EBRO DELTA, SPAIN, WHERE MALARIA HAS NATURALLY DISAPPEARED
Housing has evidently had little influence on malaria

screened almost to the same extent in non-malarious as in malarious districts shows how greatly the concomitant advantages of the elimination of bed-nets and the exclusion of flies and other insects are appreciated. The almost complete disregard of this form of protection in Europe, or by Europeans in the tropics, is all the more remarkable. Considering that H. Carmichael Lowe captained the group which lived healthily at Ostia all one summer and thus provided the original, definitive, and brilliantly successful test of the value of a screened dwelling in a malarious locality, it is curious, to say the least, that the British have taken little further interest in the method. The following paragraph, culled from the Second Report of the Malaria Commission, is astounding to any one acquainted with Panama or the modern houses built by the Italians in connexion with the 'bonifications': 'The principles on which houses should be constructed so that they may afford as little shelter as possible to mosquitoes are now well known everywhere, and it ought not to be an insuperable task in Europe to design houses for the poor in accordance with them, and to enforce their construction by degrees.'

The desirability of screening these model houses was, I am sure, not even remotely present to the author of that paragraph. This was not because of the cost. Le Prince informed the Malaria Commission that screening costs $8·50 (about 34*s*.) a house and lasts four years. It was written under the influence of a theory, which has no scientific justification, that the proper type of house would not require mosquito-proofing. Malaria is thus summarily classified among the verminous diseases like typhus and plague, which are automatically banished from cleanly houses and communities. But malaria infection is not focal in this sense, clinging to certain houses which offer special inducements for the sheltering of anophelines. Owing to the enforced mobility and nightly dispersal of these insects, whose principal aim in life is reproduction, an infected

mosquito could never, except by the merest accident, have acquired its infection in the bedroom or other shelter in which it is captured. The studies of Barber and Rice[1] on *elutus* in Macedonia make this very clear. Infected *elutus* were found in stables nearly as often as in houses. The infection of infants occurred everywhere in the village, although *elutus* density was much greater in certain shelters than in others. In particular the authors held under observation for several years two different types of house intermingled in the same village—old houses, commonly with thatched roofs, dark, moist, and in bad repair, and new houses, better lighted, better ventilated, and more tightly built. With regard to density, infection, and human blood in the stomach, the *elutus* taken in old and in new houses showed no important differences constant over two years. The proportion of infants infected was not significantly higher in old houses than in new. 'The results on the whole do not offer much encouragement to the hope that improvement in housing other than by screening would be an effective antimalaria measure in this region. . . . In summary we are inclined to believe that in this region there are only two kinds of house important in malaria, the unscreened and those provided with screens and with people disposed to use them properly.'

Christophers and Missiroli reviewed the whole subject in a report on Housing and Malaria presented to the Commission in 1933. The conception (states the report) that a dark, damp, and dirty house suffers from malaria in proportion to its attractiveness to anophelines is against the general trend of opinion. The places where anophelines congregate in the daytime give no indication of where they are likely to be found at night. 'There seems no doubt', concludes the report, 'that screening is the only really effective means of controlling malaria through housing.' It requires, of course, suitable houses, a certain intelligence on the part

[1] *Am. Jl. Hyg.* **22** (3): 512, Nov. 1935.

of the inmates, some help perhaps (technical rather than financial) from the government, and systematic inspection. They suggest that screening is particularly necessary to pioneers getting a foothold in an intensely malarious place, for conserving labour or highly paid personnel and for tiding over the years when mosquito production is unhampered and cattle are few.

This, it seems to me, hardly goes far enough. We should strive to make screening an integral and permanent part of every home built in a malarious district, whether it is in the pioneer stage or not. The whole population, and not merely the more valuable portions of it, should be protected, nor should we hold out any prospect that screening can ultimately be discarded after it has tided the community over a dangerous period. All the defects of screening come from its misuse, and no sound argument therefore can be brought against it on the count that it has often failed to accomplish its end. It does not, as far as we can find out, increase the degree of infection to those who are too ignorant or careless to employ it efficiently, as does the abuse of other serviceable things such as irrigation or water impounded to run mills. Buxton once went so far as to say, 'Screening of houses, kitchens, and larders is not recommended, for it turns them into fly-traps', and a similar objection has been raised to mosquito-proofing. Screened dwellings have often been referred to as anopheline traps, which of course most of them are, in different degrees; but there is no evidence that this increases the transmission rate in the community. Shannon observed the fate of 1,500 anophelines which had entered or were introduced into screened rooms, some vacant, some inhabited, and one into which he put a pig. None lived as long as six days. All experiments prove that imperfect screening, no matter how bad, keeps out more anophelines than no screening at all.

With populations under a certain degree of discipline mosquito-proofing of quarters has frequently been the

essential measure of malaria control, as in Panama, the great 'bonifications' of Italy, and in the United States. It is now beginning to replace bed-nets in other parts of the world. Except for temporary service, or in primitive dwellings impossible to screen, bed-nets are a nuisance and an anachronism and will not be carefully used. It is always a discouraging and thankless task to try to make even the most intelligent people take precautions against infection. Mothers will sometimes do it for babies, and Russell believes that among the native peoples of the Philippine Islands education and propaganda may in time lead to a partial use of nets. As with screening, no matter how badly they are used, they always hinder the access of mosquitoes and afford an opportunity to kill the insects which have succeeded in entering. But screening has the advantage over bed-nets in the lower temperatures it affords at night, and in permitting the use of electric fans. Broad verandahs and screened open-air recreation pavilions comfortably solve the problem of protection between sundown and bed-time. The first large installations to my knowledge in India replacing bed-nets were at Lahore and Amritsar in 1926, after twenty-five years of unsuccessful experimentation with other measures.[1] The average yearly admissions to hospital for malaria among the troops over the three preceding years were 706 per thousand at Lahore cantonments and 826 at Amritsar. A single company of 227 effectives, transferred from Amritsar in 1926 to a healthy station, furnished 196 relapsing cases, which means that practically the whole company was useless for the greater part of a year. The first season in mosquito-proofed barracks reduced the malaria admissions to one-quarter of the three-year average at Amritsar and to one-fifth at Lahore. Almost four times as many cases occurred in barracks left unscreened for comparison. In the second year of protection the incidence at Lahore fell to 46 per thousand. It is a pity it had not been done twenty-

[1] Hanafin, J. B., *Jl. Roy. Army Med. Corps*, **51** (2): 127, July 1928.

five years before. More recently the Royal Air Force has screened its 700 men at Karachi, with the result that the malaria rate per thousand fell from an average of 123 before

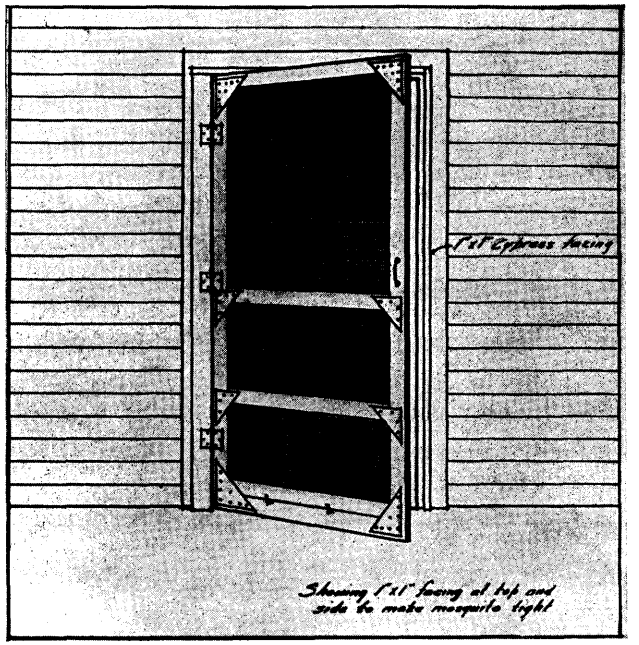


FIG. 38. A CHEAP AND DURABLE SCREEN DOOR.
(*After* Riley, G. E., *The Screening and Mosquito-proofing of Houses*, Bull. 4, Bur. of Communicable Dis., Mississippi State Board of Health, Jackson, Miss.)

protection in 1926, 1927, and 1928 to 32 in 1929, 20 in 1930, and 10 in 1931.[1]

How much can be accomplished by mosquito-proofing alone in an ordinary village whose population is not under discipline? M. C. Balfour[2] began such an experiment in 1931 in a refugee village in Greece. The town of Nea Carvali, with its population of 1,050, consists of 284 houses which were built without the least idea of making them

[1] Iredell, A. W., *Jl. Roy. Army Med. Corps*, **60** (1): 33, Jan. 1933.
[2] *Riv. Malariol.* **15**, sec. 1 (2): 127, Mar.–Apr. 1936.

mosquito-proof. For the screening operations the best material was used, consisting of bronze wire gauze and Swedish pine. Each screen-door cost 220 drachmas (a drachma is a halfpenny) and each window-screen 60 drachmas. Some of the rooms and most of the halls were not ceiled, so that it was impossible to screen them. But screened bedroom space was provided for each family. The entire cost per house, including the mosquito-proofing of floors, walls, and ceilings, was 650 drachmas or about £1 6*s*., somewhat less than Le Prince's estimate and only about three times the annual expenditure per family for quinine.

The precipitation test shows much less human blood in the anopheles after screening than before. In the unscreened parts of the houses 9 per cent. of the tested *elutus* contained human blood as compared with 57·6 per cent. in houses in unscreened villages. Dissections of mosquitoes for malaria parasites are also encouraging:

	No. of elutus	*Per cent. with sporozoites in salivary glands*
Screened rooms . . .	724	0·6
Unscreened rooms . .	1,368	1·2

These figures give no support to the theory that screened rooms are traps confining infected mosquitoes until sporozoites are formed.

As for the malaria, the most striking effect has been on the infant infections. In 1931, prior to the screening operations, 47 per cent. of the babies became malarious before they were one year old, but in 1935 none was found infected. The average spleen retired from a position below the umbilicus to a point near the border of the ribs, and the typical parasite of the population became quartan instead of *falciparum*. The extent of the improvement is shown in the following table:

Spleen and Parasite Indices, Nea Carvali, based on an examination of all the schoolchildren from 5 to 14 years of age

	Enlarged spleens	*Parasites found*	*Infants found infected*
	%	%	%
1930	100	23	..
1931	100	28	47
	Screening installed		
1932	100	29	8
1933	93	22	6
1934	82	24	2
1935	63	8	0

If there were no comparison areas we should be tempted to attribute this entirely to screening. But the intensity of malaria has been decreasing over the whole region owing to a long succession of dry years. Until the next epidemic occurs we shall not be able to say whether such a protected village can hold its advantage through an unfavourable season. We can already say, however, that it is possible to screen at a moderate cost any village with reasonably well-constructed houses, such as one would find in Greek Macedonia. The protective value and duration of this screening will depend on the education of the population and the constant inspection and repair of the mosquito-proofing itself. In Italy this is often done by the children, who learn in school how to repair holes in screening and, as their home-work, apply this knowledge to their own houses. In a country with a peasant population as intelligent and as well housed as that of rural Italy, there are no peculiar difficulties in the generalized application of the mosquito-proofing of dwellings, to be combined if possible with the regular employment of insecticide sprays. In Holland, for example, this may prove to be the only effective antimalarial measure. The investigations of Swellengrebel have now shown that anophelines are infected in north Holland after 15 August, when they cease to lay eggs and become 'fixed' in houses for

the winter, but before 1 November, when such infections as have been acquired are no longer dangerous owing to the degeneration of the malaria organisms in the mosquitoes. A campaign waged not by the peasants themselves but by trained men with power sprays, in the 'malaria' houses during this period of ten weeks, might show conspicuous results.

Under far different circumstances the same measure has been applied in Natal and Zululand to native huts in rural areas infested with *gambiae* and *funestus*, where antilarval work is out of the question. Park Ross[1] describes how the idea arose, as an emergency measure, on a few estates, and the striking improvement which almost immediately followed:

	Estate A (*all huts sprayed*)		*Adjoining Estate B* (*no spraying done*)	
	Pop.	*Daily sick rate*	*Pop.*	*Daily sick rate*
March 18, 1931	120	35	250	40
Mid-April	120	10	250	60
End of May	120	5	250	60+, with 10 deaths

Medical attention was identical on the two estates. The work was then organized on a large scale. Mosquito-proof doors were provided for each hut, the schoolmasters were all instructed in the programme, and the huts were then sprayed with a pyrethrum insecticide, at first daily, then weekly. In 1934, 18,000 huts were sprayed regularly at a cost of 1·4*d.* per hut, and in 1935, 45,000 huts were under control, with 9 European inspectors, 60 native assistants, and 300 sprayers. Malaria has diminished accordingly. In 1932, an epidemic year, there were 10,000 deaths; in 1933, 1,000; in 1934, 882, and in 1935, 119. The last season has been characterized by a minimum of fever and less anopheline breeding. Fever has been absent from areas never before known to be free. It remains to be seen what the effect of the next epidemic year will be.

[1] *Quart. Bull. Hlth. Org. L.o.N.* **5** (1): 114, Mar. 1936.

FIG. 39. THE REFUGEE VILLAGE OF NEA CARVALI
All the bedrooms are screened. (See p. 295)

FIG. 40. LARVICIDE GANG AT TIRANA, ALBANIA
All breeding-places which cannot be permanently eliminated within 4 kilometres of Tirana are dusted weekly with Paris green

An interesting sidelight has been thrown by this experiment on the vexed question as to whether mosquito control, by disturbing the acquired immunity of a highly infected group, may not do more harm than good. 'We have felt diffident', writes Park Ross, 'about applying insecticidal control on a grand scale to native areas infested with both *funestus* and *gambiae* lest any degree of immunity acquired by the native population be impaired. Circumstances drove us in 1933 to use insecticides for barrack control in such areas as being the only economic procedure available. This has been continued ever since and its success has been such that one need have no hesitation in applying insecticide control to the general native population in such areas.'

3. *The Use of Larvicides*

The principal usefulness of larvicides, such as Paris green or oil, is the possibility they frequently offer of bringing malaria transmission rapidly under control while the engineers are attacking the breeding-problem in a more permanent but piecemeal fashion. The aeroplane has extended their application to the larger breeding-places, although this method has been regularly adopted only by the Americans and Russians. It is rarely that the use of larvicides can be abandoned entirely even after the drainage programme has been completed. In areas of *A. superpictus* and other stream breeders the engineers can sometimes do nothing to improve the situation, and a permanent larvicide gang becomes necessary to carry out the disinfestation of surface waters year after year. The objection made to this method in the beginning in Italy was that it produces no lasting effect. 'No victory is real', said Gosio, 'that does not overcome the endemicity of the disease and suppress its source. Failing this we have only scotched an enemy whose reawakening is an ever threatening possibility.' But the application of larvicides to water-surfaces differs in no essential way from

the application of insecticides in agriculture. The farmer must ever be fighting his insect enemies without any prospect of final victory. He dusts the crops because his living depends on it, and he does not dust the water because only his health depends on it. 'The serious objection to antilarval measures in Europe as in the tropics', states the Second Report of the Malaria Commission, 'is their difficulty and expense.' Unfortunately there is no easy road to malaria control. The 'direct' methods urged by the Commission, of attacking the parasite in the blood and in the mosquito, have been repeatedly shown to be even more difficult and expensive, and have given only mediocre results.

The answer to most of the criticisms is that in spite of theoretical difficulties larvicides are now in wide and increasing use everywhere in the world. They are the principal dependence of rural centres of population over great areas in the Mediterranean Basin, especially in southern Italy, where there is hardly a malarious village without its larvicide service. Such control to be effective requires a good foreman with some of the qualifications of a British sanitary inspector, trained in anti-mosquito work. The entire cost of protecting an average Calabrian village, including inspection, does not exceed £100 a year, which comes fractionally from a number of different sources. This is usually about half the previous cost of treating the population for malaria. What is needed to start the process in any region is a successful demonstration, which is invariably followed by requests for the extension of the service to other communities, until eventually it is made obligatory and a large part of the cost assumed by the local governments, or assessed, as in parts of Italy, on the local landholders.

The encouraging thing about larva control is its cumulative action. The same measures applied year after year give increasingly satisfactory results. Here, for instance, are the

anopheline catches over a period of years at Mourla, a village of the Peloponnesus:

	Total anophelines	*No. of weekly catches*	*No. of stations*	*Average weekly catch per station*
1930—observation year	2,044	21	14	7
1931—larva control	1,147	28	14	3
1932 ,, ,,	1,054	28	13	3
1933 ,, ,,	253	28	13	0·7
1934 ,, ,,	102	28	13	0·3

Most of our stations would show the same thing. It is due, apparently, not so much to a gradually improving technique as to a constant reduction in the number of mosquitoes entering hibernation each winter. If this is so, no great autumnal invasions can be taking place from outside, as described by Kligler in Palestine and Herms in California.

There is a parallel decrease in malaria. Here are the data for the town of Fiumicino on the Tiber delta:

Results of 10 years of mosquito control in Fiumicino

Year	*Population*	*Malaria cases per 1,000 of population.*	*Anopheles found in catching stations*
1921	3,300	221	Unknown
1923	3,400	360	,,
1925	3,500	232	,,
Larva control begun by Malaria Experiment Station			
1926	4,000	94	5,132
1927	4,500	30	1,488
1929	4,500	26	312
1931	6,000	14	53
1933	8,300	6	1
1935	8,500	2	1

This was the scene of Grassi's early experiments, and we have an almost complete record of malaria incidence since 1918. In the early years every increase of population was followed by an increase of primary cases. Since antilarval

work was begun in 1926 the population has again more than doubled but without a rise in the new cases. The health officer fears neither the immigration of non-immunes nor that of gametocyte carriers, both of whom have flocked to Fiumicino to occupy new land, without disturbing the steady downward course of the malaria endemic towards complete extinction. Fiumicino has now come to be a popular sea-side resort where thousands sleep in unscreened rooms without danger.

4. *The Permanent Elimination of Breeding-places*

The Balkans are the most malarious part of Europe. While politics, religion, and social usage combine to complicate life to an unusual degree in this restless corner of the world, the physical conditions under which men live and work are extremely simple. They are, in fact, over large areas, harsh and primitive, and resources are correspondingly meagre. Antimalaria work must be carried out with the means at hand and with the funds locally available. Great engineering enterprises are not lacking, such as the reclamation of the Vardar and Struma valleys in northern Greece—schemes with a vast agricultural objective whose financing and execution lie outside the budgets and personnel of departments of public health and of public works. The ordinary problems of anopheline breeding which in their endless variety beset the malarious villages of the Balkans are of a different magnitude and must be solved, if at all, by ingenuity and imagination rather than with the expensive and mechanical aid of modern engineering machinery. It is precisely when dealing with a primitive people under such conditions that a permanent solution should be sought for each malaria problem, even if the initial expenditure may seem somewhat disproportionate and likely to limit rapid extension of the programme. Little reliance can be placed on the ability of the local populations to maintain complicated larvicide services year after year,

FIG. 41. LARGE PARIS-GREEN BLOWER, PALANQUIN TYPE

FIG. 42. ABOVE BLOWER BEING CARRIED ACROSS AN EXTENSIVE MARSHY AREA

FIG. 43. PARIS-GREEN DUSTING BY AEROPLANE
(By courtesy of U.S. Navy Dept., Bureau of Medicine & Surgery, Washington, D.C.)

FIG. 44. TYPE OF TORRENTIAL BED CONTROLLED BY PARIS-GREENING (BERAT, ALBANIA)

and, in the long run, permanent measures may be the least expensive. 'Good drainage', said Mr. R. J. Bee to a meeting of Malayan engineers, 'is cheaper eventually than other methods of mosquito control, for the capitalized cost of effectively spraying a swamp with oil once a week over an extended period of say twenty years would be enough not only to drain the swamp but to build a very fine house upon it.' There are often, I might say always, accessory advantages, as well, to malaria drainage. Earle[1] has underdrained the sugar plantations of Puerto Rico at considerable expense, as an antimalarial measure. But these subsoil drains are already justifying themselves in other ways. Alkali is washed out of the soil and taken away, the soil is aerated, the drains can be ploughed over, and the crops are increased. Such drainage may prove to be a profitable investment and not a loss. While no one would be likely to contest this, there is nevertheless a rather low limit in the Balkans to the amount of money which can be raised all at once in a village to carry out a drainage project. Under such circumstances the essence of good engineering lies not so much in developing a sound and straightforward plan of action along classical lines, as in devising some way of eliminating a dangerous breeding-area with the simplest of mechanical means and for a sum which is evidently ludicrously inadequate.

Nothing appeared more unlikely at first sight than that any cheap and easy way could be found in Albania to stop or even restrict anopheline breeding round some of the principal centres of population. Tirana, the capital, lies between two rivers, one of which in summer turns into an interminable series of clay-bottomed pools linked by a thread of flowing water, while the other is one of those torrential streams so characteristic of the Balkans, which by erratic changes of its course from one winter to the next spreads its gravelly bed over a zone hundreds of yards in

[1] *Puerto Rico Jl. Pub. Hlth. & Trop. Med.* **11** (3): 434, Mar. 1936.

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(By courtesy of U.S. Navy Dept., Bureau of Medicine & Surgery, Washington, D.C.)

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width, in every depression of which water may come to the surface to form a paradise for *superpictus* larvae. For 7 kilometres such a broad white band of water-bearing gravel lies within easy flight range of the city. That is why it used to be the custom of the Diplomatic Corps to absent itself from Tirana *en bloc* during the entire summer.

Durazzo, the port, 40 kilometres away, has an even more unfortunate situation as regards malaria. It was built ages ago for security on a ridge jutting into the sea, separated from the mainland by an extensive lagoon. The original description we received of this place was rather encouraging, for it particularized a great number of small breeding-places along the foreshore and among the dunes to the south, with only incidental references to the lagoon. This, however, on inspection turned out to be 20 square kilometres of marsh hardly more than half a metre deep and crowded with subaquatic and emergent vegetation. Durazzo was like the soldier found on the battle-field whom the nurse reported to be suffering from a number of superficial wounds easily curable in seven to ten days, and from only one which she thought would certainly be fatal. Over 19,000 anophelines were collected on a single day from eight stables at the periphery of the town, and I remember being greatly impressed, on the occasion of my first meal in Durazzo, at being able to count thirty-seven anopheles on the nearest wall without moving from my chair. Few strangers cared to remain in Durazzo overnight between July and October. Valona, a southern port, presents still another problem, separated from the sea by a chain of shallow marshes among the dunes, most of which are below sea-level.

The task confronting the malariologist, the drainage engineer, and the entomologist in Albania is to put a stop to malaria transmission in situations like these without the aid of excavators, suction dredges, or even a concrete-mixer, and to keep within the limits of a drainage budget which never has exceeded 25,000 Swiss francs a year. Fortunately

this money is ear-marked for prevention. It cannot be impressed into the service of medical assistance however urgent the need. And furthermore there is no time-limit, although the civil authorities, being characteristically human and ignorant, often show an understandable impatience. Malaria has taken its toll of Albania for two thousand years, yet it seems intolerable that it should require a decade or so to get rid of it. But 'perfection and speed in any line of human endeavour are expensive', as Russell says. We have striven in Albania rather for the 'continuity of modest effort' which he recommends.

Malaria control, as Clarkson once said—and this applies particularly to minor drainage in the Balkans—'does not cost money, it costs labour'. The first attack, then, on the high cost of antimalaria work was to endeavour to enlist an army of free labourers. This turned out to be more feasible than it sounds. Bulgaria, denied an army by the treaties of peace after the World War, organizes her young men annually into an army of labour for public works, and it is with this force that most of the permanent drainage work of the Strumitza valley has been done. In Albania, once the idea was broached, many suggestions were forthcoming. The king himself proposed that since the young women were accustomed to working in the fields beside the men, they might be organized for antimalaria work during the time their brothers were engaged in obligatory military service. Soldiers themselves have often been used to protect, by antilarval measures, the villages in which they are stationed. The most useful plan has been to apply the *corvée* system to malaria control and to divert citizens, electing to work out their taxes, from road-building to minor drainage. In this way, in the course of a dozen years, the sand dunes of Valona may possibly be moved into the marshes, permitting it to become the health resort which nature planned and *elutus* ruined. Persistence is the motto, not speed.

X

The rivers at Tirana presented an entirely different problem. Four men could dust them with Paris green in six days, and repeat the operation weekly from April until October, rendering them innocuous as a source of anophelines; but this was far from being a satisfactory solution. Such torrential rivers remain on the whole the principal unsolved problem in malaria control in Europe. It would be hard to know how to put gangs of free labour usefully to work on these immense torrent beds, which sometimes measure half a kilometre in width. The Tirana river does not rise from permanent springs of any great size, and its summer flow is normally less than 3 cubic metres a second. Of this a small amount was diverted by the peasants at various points for irrigation, and the more the river was reduced in volume the more dangerous it became as a *superpictus* breeding-area. It was decided to prepare a single large irrigation system capable of receiving the entire summertime flow of the river, taking the water out well above the city and turning it back below so that the whole bed could be dried up for at least 7 kilometres. Part of the water could then be turned intermittently into the other river to sluice it down, although ultimately barrages will be constructed on the Malayan principle which will automatically impound the small but permanent flow and regularly release it to flush the larvae out of the pools in its bed. The Ministry of National Economy was then approached on the question of providing the funds for the irrigation ditches as well as for the construction of the dam, a concrete sill across the river at a favourable point which would offer no obstruction to the water in flood but would divert it in summer into the main canals (see Figs. 45, 46, 47). As was expected, the funds were made available when upon examination it was found that the value of the water, if used for irrigation, would pay for the entire project in four or five years and would thereafter yield a considerable profit. This is the second way of reducing the cost of malaria control, capable of a thousand

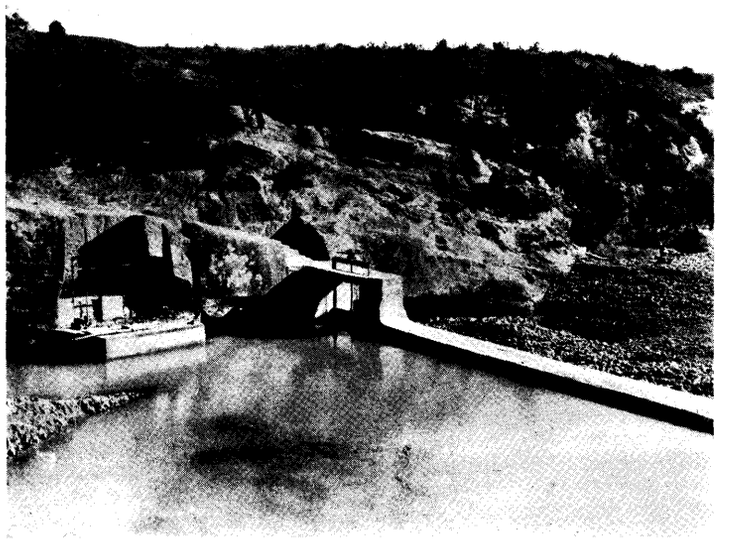

FIG. 45. BARRAGE ACROSS THE RIVER TIRANA (ALBANIA) TO DIVERT THE ENTIRE SUMMER FLOW INTO THE IRRIGATION SYSTEM

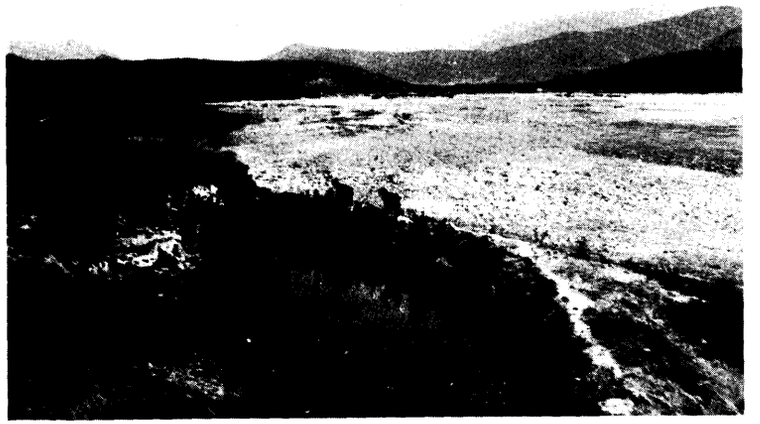

FIG. 46. DRY BED OF THE TIRANA RIVER JUST BELOW THE BARRAGE, WITH IRRIGATION CANAL IN FOREGROUND

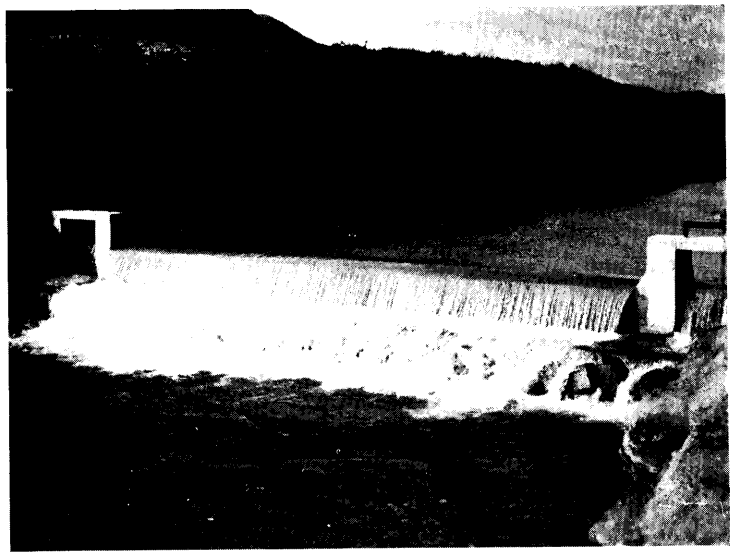

FIG. 47. WATER FLOWING OVER TIRANA RIVER BARRAGE IN WINTER

FIG. 48. TYPICAL ISTRIAN STOCK-POND WITH ANOPHELES BREEDING CONTROLLED ENTIRELY BY GAMBUSIA
(Rovigno, Italy)

applications: disguise it as an agricultural or economic programme and tap sources of funds not available for pure sanitation. Antimalarial drainage will more often than not create values which would make it worth doing even if there were no malaria problems to solve.

There remained the vast and terrifying lagoon at Durazzo. The muddy river Arsen which flows into the sea not many kilometres away could be turned into the marsh and would eventually fill it up. Perhaps this will be done some day when there develops a certain pressure of population on land, but not with the modest budget of the Malaria Bureau. A canal existed between the lagoon and the sea at the southern end, but it failed to drain the marsh because most of the area was below sea-level. The plan was conceived of forcing the sea into the lagoon in order to replace the fresh water with salt water. No claim to originality can be made for this idea, now that Professor Missiroli has succeeded in tracing it back at least to St. Thomas Aquinas,[1] who wrote, with respect to malarious regions near the sea: 'By means of ditches the standing water can be drawn towards the beach and there the sea, in times of tempest inundating the marshes, will not permit the development of animal life in the marsh, and if living things are introduced from higher regions they will be killed by the abnormal salinity.' But this ingenious and practical suggestion made in the thirteenth century seems to have waited overlong for its application. Nor was any precipitate action taken in the present case, since the most dangerous anopheline in Albania is a brackish-water breeder, and unless the salinity could be brought above the toleration point for *elutus* and held there throughout the summer the situation might easily be made infinitely worse rather than better. Studies carried out over two years on *elutus* breeding-places showed that the Albanian insect was unable to carry through the entire development from egg to winged adult in water containing more than 2·2 per cent.

[1] *De regimine principum*, book 2, ch. 2.

of salt, whereas the water of the Adriatic Sea runs normally to 2·9 per cent. or even more. The margin was not great, but there was another consideration. All lagoons along the Albanian coast sufficiently open to the sea to acquire its salinity, even for part of the year, are bare of aquatic vegetation; and no anopheline can breed in open water.

A canal was finally dug through the low dunes at the northern end of the lagoon and extended 30 metres into the sea through three lines of concrete tile a metre in diameter. At the end of these pipe-lines a concrete basin was constructed resting on the sea bottom, and pierced for automatic iron gate-valves opening inward. There is ordinarily not more than a foot of tide in the Mediterranean, but often a south wind will pile up the water for days in the Adriatic and thrust a considerable amount of water through the valves into the lagoon, eventually forcing an equal quantity out through the opening at the south end, 9 kilometres away. In the course of a single year this intermittent addition of salt water brought the salinity of the entire lagoon well above the desired level. The salt water is apparently drawn into every far nook and corner by the high evaporation rate of a sheet of shallow water open to the subtropical sun and warm breeze for many rainless weeks. No breeding occurred in 1934 and 1935, and malaria transmission ceased entirely. The inlet valves provide sufficient head for the extensive water system, every part of which is at sea-level. The southern outlet, however, turned out to be equally important to the circulation. This was allowed to silt up in 1936, which kept part of the lagoon fresh enough for *elutus* breeding for a short period at the beginning of summer.

The cost of the canal and inlet was about 20,000 Swiss francs, to which the town as well as the State contributed. But there was an unexpected denouement to the story. The constant inflow of fresh sea-water and young fish produced optimum conditions for fish-culture in the deeper central

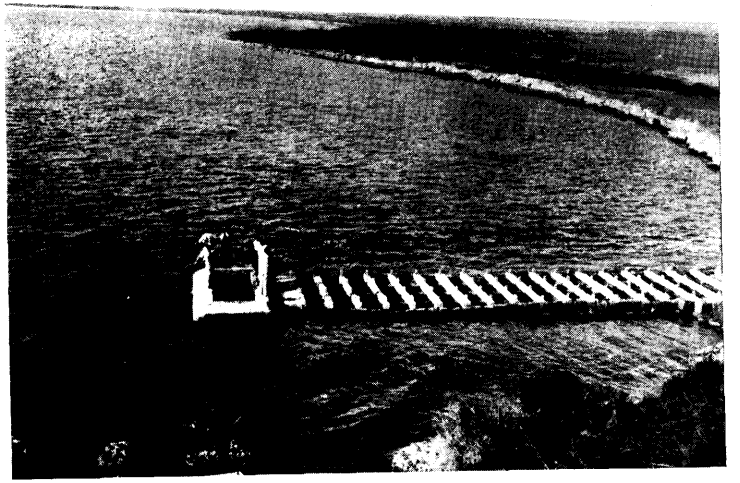

FIG. 49. SEA-WATER INTAKE OF THE CANAL AT PORTO ROMANO FOR THE SALINIFICATION OF THE DURAZZO LAGOON (ALBANIA

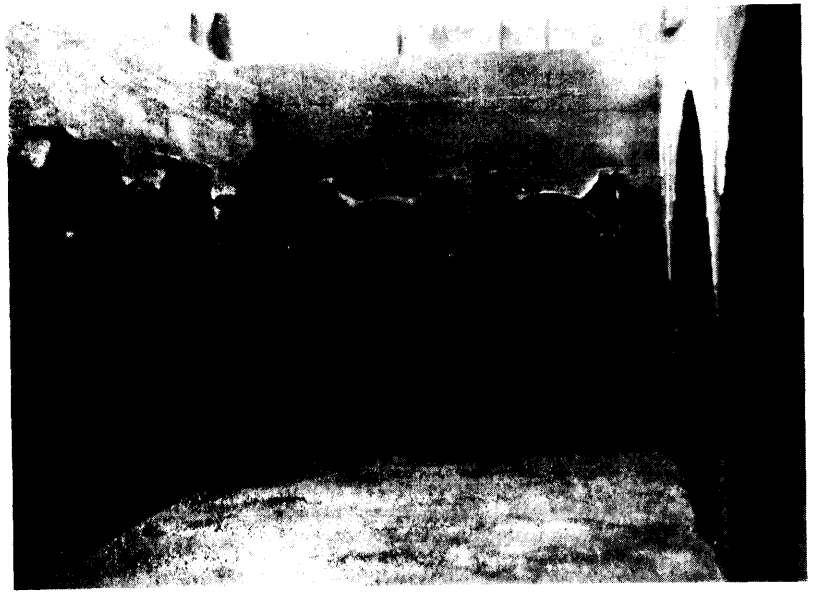

FIG. 50. INSIDE THE INTAKE BASIN, SHOWING THE INLET VALVES ON THE LEFT AND THE MOUTHS OF THE TILE LINES ON THE RIGHT (DURAZZO LAGOON, ALBANIA)

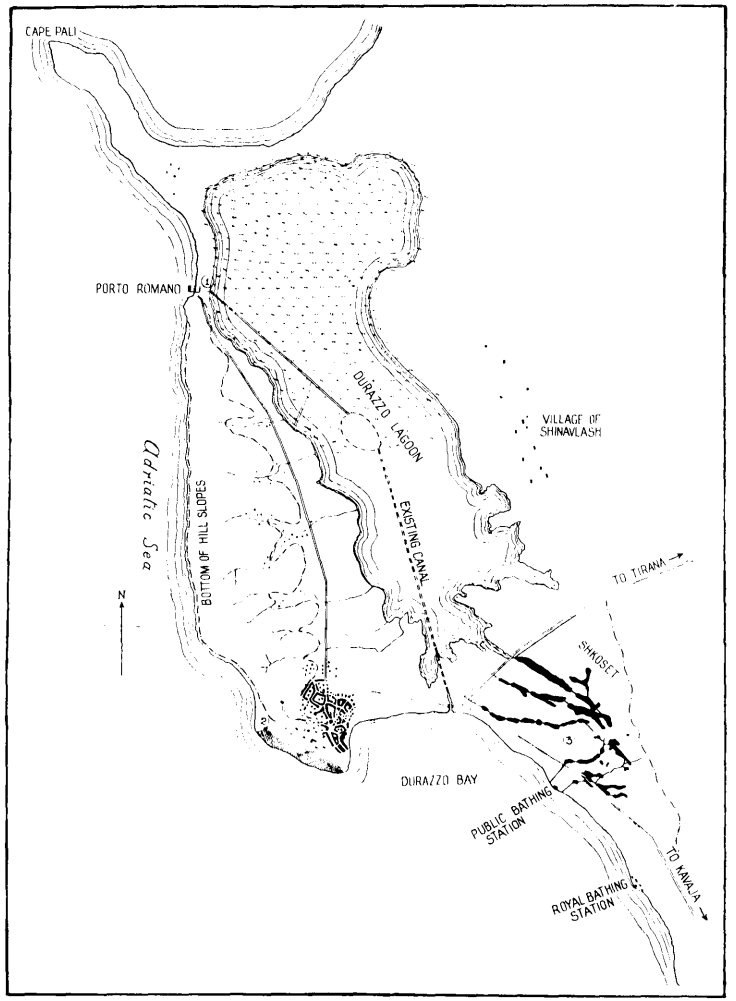

FIG. 51. CHART OF THE DURAZZO LAGOON (ALBANIA) SHOWING THE LOCATION OF THE CITY AND THE INLET AND OUTLET OF THE SALINIFICATION CANAL

(1) Salt-water intake with valves.
(2) Marshy foreshore, now filled.
(3) Group of brackish ponds, drained and filled.

Scale: 1 inch = ca. 2 miles.

portion of the lagoon, and a private company paid 2,000 francs for the privilege of putting traps in the new canal. The concession now pays the Government annually an amount of money almost equal to the entire cost of the project. Up to the present time, therefore, we can say that the expenditures for malaria control in Albania have been a profitable investment. The salinification of the Durazzo lagoon has been described here, however, to illustrate, not the economic advantage which may often be derived from measures to control malaria, but the fact that the biologist can help the engineer to set up a natural check on anopheline production which may be far less expensive than outright elimination of the water body. This is the third, and in its vast potentialities the most important, method of cutting the costs of malaria control. Unfortunately our knowledge of the range and mechanism of such checks is only fragmentary. The principal object of malaria field studies to-day is the understanding and application of natural methods of control. 'With nature continually demonstrating that mosquitoes can be naturally controlled without our help', writes Senior White, 'we look enviously towards these costless methods.' Our space permits only a hasty and superficial glance at a subject which should occupy an entire volume.

5. *The Biologist in the Field of Malaria Control*[1]

It may be objected that salt water acts as a larvicide in the Durazzo lagoon and not as a 'naturalistic' check on anopheline production. We do not, in fact, know how the salt acts. The larvae of *elutus* become hard to find as the salinity reaches sixteen parts per thousand, which is far below their limit of tolerance in the laboratory. Possibly the plankton on which they feed and certain grosser forms

[1] Williamson, K. B., 'The Control of Rural Malaria by Natural Methods', *L.o.N. Eastern Bureau*, Singapore, 1935–6, with references and notes, series 1–3, separately bound.

of subaquatic vegetation in the lagoon are more sensitive to salt than the larvae. The lack of one and the decomposition of the other may render the water unfit for larval existence even before the salt becomes directly lethal.

There are, of course, better examples than this of the establishment of a perfectly natural check on anopheline production. On the Tiber delta, about two and a half miles from the town of Fiumicino, there used to be a large marshy area marking the spot where the Emperor Trajan once constructed a port for the city of Rome. In 1918, when Grassi set up his 'malaria observatory' in Fiumicino, it was generally supposed by malariologists that it was enough to control anopheline breeding for half a mile or at most a mile round about centres of population, since this had been the experience everywhere in the tropics and also in the United States. It produced so little result at Fiumicino, however, that Grassi, who had always been suspicious of the marsh, stained a large number of anophelines with a blue dye and set them free at Trajan's port. Some of them turned up in due time at Fiumicino, and Grassi discovered that he had a much greater problem on his hands than he had expected. His first impulse was to attempt to drain the marsh, but the engineers reported that it was at sea-level and pumps would have to be used to put the water into the River Tiber, which was close by, flowing between high levees through the flat land of its delta. After some thought Grassi suggested to the owner of the land, who was Prince Torlonia, that he should construct a revetted embankment round the marsh and fill it in winter with water from the Tiber which could be used during the summer for irrigation purposes. The Prince, upon investigation, found that this would be a profitable enterprise and undertook to carry it out. Grassi unfortunately died before it was completed, and upon taking over Grassi's station at Fiumicino we were disappointed to find that the lake surface was covered in the shallow areas with a dense aquatic growth rooted in the mud and protecting in-

FIG. 52. TRAJAN'S LAKE (TIBER DELTA) BEFORE REVETTING AND THE IMPOUNDMENT OF WATER

FIG. 53. TRAJAN'S LAKE AFTER REVETMENT, SHOWING ABSENCE OF AQUATIC VEGETATION

FIG. 54. TYPICAL STREAM (*MARANA*) OF THE ROMAN CAMPAGNA

FIG. 55. METHOD OF TREATMENT OF A STREAM BY TRAINING, IN ROMAN CAMPAGNA

numerable anopheline larvae from wave action and from minnows. Prince Torlonia then installed a pump, with which he raised the level of the lake, and within three years all the vegetation had disappeared, owing to the increased depth and to the rapid and considerable fluctuation of the water-level in summer. Trajan's Lake is now an open body of water free from anopheline larvae at all times and requiring no larvicide treatment. It irrigates about a thousand acres of land which were previously uncultivated. This is an excellent example of the highest type of antimalarial engineering. The biologist, instructing the engineer, has secured the complete cessation of anopheline breeding with a concomitant benefit to agriculture that has not only absorbed the cost of the project but has even created a profit.

A more famous example is Walch's[1] method of controlling anopheline breeding in the fish-ponds on the coast of Java. These salt-water ponds, used for the cultivation of the 'bandeng', a fish of great economic and dietary importance, were also the cause of all the coastal malaria, affording an excellent breeding-ground for *A. sundaicus* (*ludlowi*) in the green surface algae which formed the principal food of the fish. No control had ever been attempted, and the spleen indices in the children of the near-by villages ranged from 43 to over 90 per cent., depending on their distance from the ponds. The problem was to eliminate the anopheline breeding without destroying the industry, which was both profitable and necessary. It was solved by substituting a bottom growth of *Cyanophyceae*, or blue-green algae, for the surface vegetation. Ponds were constructed so that the water could be run off periodically (first monthly, then quarterly) without killing the fish, which remained in a deep canal round the periphery. The green algae, settling to the bottom, were killed by exposure to the sun and desiccation. After two days the pond was filled again at high tide, the depth of water being regulated to permit an

[1] *Meded. Dienst. d. Volksgez. Ned.-Ind.* **19** (3): 400, 1930.

intensity of light at the bottom stimulating to blue-green algae which rapidly spread from the peripheral canals. It is needless to recount the difficulties encountered at first by Professor Walch, due to the ignorant opposition of the renters who feared the loss of their invested capital. In the end the profits were greater than before, and spleen indices at Passoeroean, the experimental area, dropped from 84 per cent. to 18 per cent. within three years.

To most persons the 'biological' control of an insect refers more particularly to the introduction of a natural enemy able to keep down its numbers. Such an enemy all mosquito larvae possess in the little fish, gambusia. 'To a minute viviparous top-minnow of the Florida Everglades', wrote David Starr Jordan in his autobiography, 'Dr. Felipe Poey of Havana gave the scientific name *Gambusia*, derived from the Spanish phrase *pescar para gambusinos*—fishing for gambusinos, that is, catching nothing.' This insignificant find of Dr. Poey has in a mere decade become the best-known, most widely sought, and perhaps the most numerous fish in the world. Conserved and protected everywhere, encouraged to multiply and given the freedom of all waters, gambusia, as Sella says, was born under a lucky star. Imported into Spain by Sella in 1922, and from there to Italy by Grassi, it has subsequently been distributed by the Malaria Experiment Station in Rome all over Europe, to Australasia, Africa, India, and the Far East. It devours all kinds of mosquito larvae, it adapts itself easily to every climate and every kind of water, fresh or salt, and it is extraordinarily resistant to all sorts of untoward circumstances, being usually the last thing alive in the muddy bottom of a drying waterhole. It is particularly easy to cultivate in any likely pool or tank (although in Ceylon, according to Russell, the nurseries have to be screened on account of the lupa fish, which travels overland in search of food!). Its rate of increase is spectacular. Sella has estimated that in Istria, where it has been particularly successful, one hibernating

female may give rise to over 4,000 new individuals during the course of the summer. It seems to suffer from no epidemic diseases. It is never, as far as I know, a nuisance. It is that ideal biological agent which has few enemies except small boys and harms nothing but mosquito larvae.

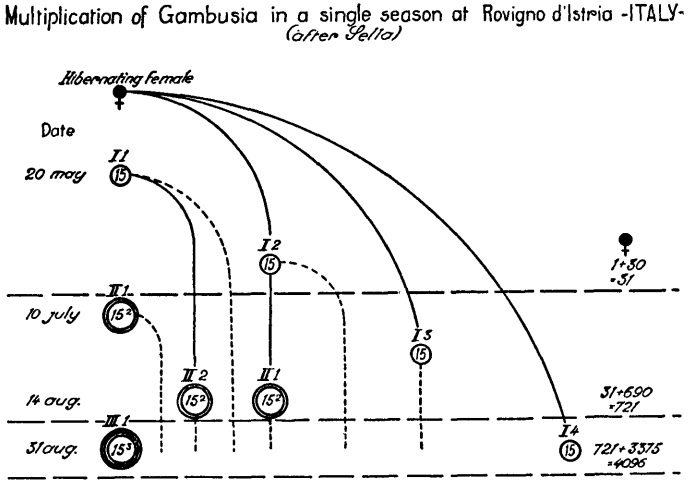

FIG. 56. CHART SHOWING THE MULTIPLICATION OF GAMBUSIA IN A SINGLE SEASON (*After* Sella).

There are native fish in every country which eat larvae, but none of them has had the success of gambusia, which everywhere, except in the United States, is an exotic predator. It is almost impossible permanently to increase the numbers of any indigenous species which has already come to a natural balance with all the other components of its native environment. Some years ago Dr. Campbell,[1] of San Antonio, Texas, conceived the idea that bats could be cultivated like bees and when sufficiently numerous would destroy all mosquitoes within a wide radius of the roosts which he had invented. This theory got no following in America, but a retired Italian general was sufficiently impressed to construct a bat-roost at Fiumicino. Near by at

[1] Campbell, C. A. R., *Bats, Mosquitoes, and Dollars* (Boston, Mass., 1925).

Trajan's Port are some old Roman ruins with extensive dark galleries hundreds of metres in length, a small portion of which have been occupied probably for centuries by a great number of bats. The galleries could accommodate a hundred times the present number, but the bats have reached the maximum population permitted them by nature under the local conditions. No bats, as far as could be determined, ever entered the general's roost. It may be because it is at home in the United States that gambusia seems to be least successful there. What is needed, perhaps, in America is the introduction of some strange minnow.

Gambusia is rarely sufficient, by itself, to accomplish the whole task of malaria control. But it is evident from the criticisms one hears of it from time to time that the role of gambusia has been rather generally misunderstood. As a simple larvicidal agent, this fish has a number of defects. It is tardy in getting down to work in the spring, handicapped by matted vegetation at the water-surface, and unable often to maintain effective numbers in running water. It is, however, the long-term effect on the anopheline population which counts, and this can only be appreciated after many years. Its motto is that of Paul Russell: continuity of modest effort rather than perfection. Gambusia in Europe is a new and disturbing element introduced into a delicately balanced community in which an anopheline vector is fighting to maintain itself. In Istria, a peninsula in the Adriatic Sea, the prevalent type of surface water is unusually favourable for gambusia. There are almost no rivers and a multitude of small ponds. Some years after its introduction, gambusia and anopheline larvae could frequently be demonstrated in the same pool, but ten years of unremitting pressure on the anopheline reproduction rate have brought mosquito density to a point below the threshold for malaria transmission. The effect of gambusia is cumulative. It is probable, from the frequency with which an anopheline lays eggs and the considerable number in each clutch, that the

continuity of its fragile existence in nature is due in large part to its extraordinary fecundity. At any rate, anophelines are now almost impossible to find in Istria over wide areas where the spleen index of the rural population used frequently to rise above 90 per cent. On the whole, however, gambusia will make the most impression on localities where the anopheline density is near that critical level at which the percentage of new infections in the population is equalled by the percentage of recoveries, and below which malaria can no longer maintain itself as an endemic disease.

We may expect that, as time goes on, biological restriction of mosquito breeding will play an increasingly important role in the reduction of the cost of malaria control.[1] But the biological knowledge of which the engineer is most in need is that which will enable him to avoid costly interference with water bodies which appear dangerous but are not actually sources of malaria. This information, which the ordinary engineer cannot be expected to have, is the basis of the growing practice of 'species sanitation', introduced by Watson, which takes into account the fact that only a few anophelines are dangerous and that they may breed only in certain types of water. In America *quadrimaculatus* is a pond breeder, and the type of open drainage used to put the water into motion is a biological measure adapted to the peculiar habits of the only important malaria vector. In Europe, for instance, such drainage never had any success. In Malaya the dangerous anopheline *maculatus* does not breed in ponds or marshes but only in running water on cleared land. An attempt has been made, therefore, by Williamson to reverse the ordinary procedure, turning a stream by means of dams into a succession of pools with miniature waterfalls. Much money has been saved in the Philippines by the knowledge that all the malaria vectors are upland stream breeders and that marshes, rice paddies,

[1] Senior White, R., *Trans. Far East Assoc. Trop. Med. 7th Cong.* 2: 718, 1929.

and all standing water on the plain can be completely ignored. In Italy *maculipennis* itself is both a stream and a pond breeder, so that drainage by canals and ditches has no antilarval value at all. The biologist must tell the engineer where (as in northern Italy) this breeding in ditches and canals need cause no alarm, and where on the contrary (as in the Pontine Marshes) it must be meticulously extinguished. Thus we are now actually putting into practice 'race sanitation', and it is only a step to the artificial replacement of one species or race of anophelines by a less dangerous form. In Holland the substitution of *atroparvus* by *messeae* has been going on unwittingly for centuries, as the land reclaimed from the sea becomes sweetened by irrigation. In the Pontine Marshes there are already indications that the intensive cultivation of the land, its fertilization with chemicals and manure, its irrigation with fresh water from the hills, may be increasing the proportion of the relatively harmless races of *maculipennis* at the expense of the dangerous brackish-water breeders. If so, zooprophylaxis, or the protection of man by his domestic animals, will increasingly interfere with malaria transmission.

The Pontine Marshes, as they appear to the observant visitor to-day, are in fact not only an exposition and epitome of the progress of malaria control from the earliest times until now, but are full of suggestive prophecies for the future. The name Volscian, or marsh-dweller, given to its earliest inhabitants shows that from the fifth and sixth centuries B.C. this quadrangular area of alluvial land, reclaimed by nature from the sea, has always presented an unsolved drainage problem to those anxious to develop its fertile, level acres so near to Rome. At what epoch malaria made its appearance is unknown—possibly at the time of the Punic Wars—but for over 2,000 years the plain has been uninhabitable on this account alone. While a dense agricultural population has been occupying the marshes of the

FIG. 57. HUT ON WHEELS, FORMERLY USED BY MIGRATORY FARM LABOURERS IN THE ROMAN CAMPAGNA BEFORE THE ERA OF 'INTEGRAL BONIFICATION'

FIG. 58. MODERN FARM ON THE RECLAIMED LAND OF THE PONTINE MARSHES. ON THE LEFT THE STABLE, ON THE RIGHT THE LAUNDRY, CHICKEN-RUN, AND PIGSTY

FIG. 59. FENCED AND REVETTED DRAINAGE DITCH IN THE PONTINE MARSHES

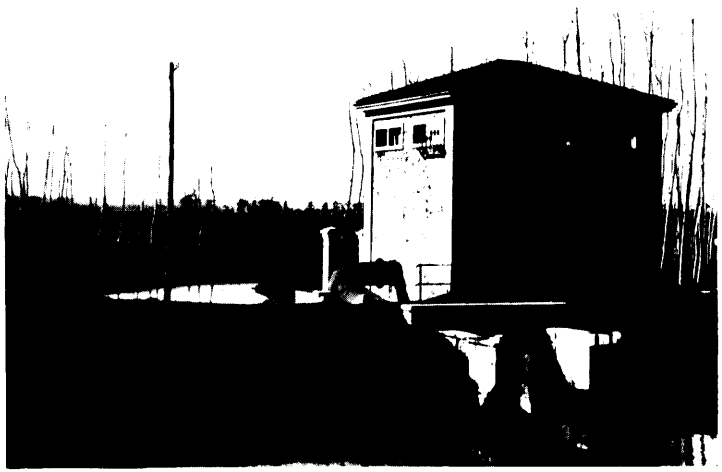

FIG. 60. ONE OF THE TWENTY AUTOMATIC ELECTRIC PUMPING STATIONS WHICH KEEP THE PONTINE MARSHES DRY

Po delta as fast as the sea could be diked out, not a single permanent habitation existed on the Pontine Marshes as recently as 1930, and every year between June and September the mud and wattle huts of the swineherds and charcoal-burners remained deserted as the migratory occupants abandoned the fever-stricken area and returned to their mountain villages. The engineers have been ready for a long time to solve the technical problems of drainage, but the doctors were unable to solve those of malaria. The example of the Po delta was a delusion and a snare. The supposed effect upon malaria transmission of adequate nourishment, modern housing, prompt medical assistance, and intensive agriculture failed to be realized in the south. The miracle of anophelism without malaria did not come to pass in the Pontine Marshes. In 1928 it began to be suspected that the anophelines in the two areas were different in instinct and behaviour, in spite of their identical appearance. In 1931 it was discovered that in fact they could be distinguished as two separate races by their eggs. In 1934 genetic studies proved them to be different species, the one a parasite on domestic animals, the other with a wide range of hosts including man.

The problem facing the engineers is therefore not only drainage but the prevention of all anopheline breeding over a marshy area of 200,000 acres, inhabited already by more than 50,000 people. This is now virtually accomplished. Most of the recommendations of the Second General Report of the Malaria Commission of the League of Nations have had to be disregarded. All five fundamental lines of attack have been employed simultaneously. Larva control has taken precedence over treatment. Lagoons, canals, and ditches are revetted and centre-channelled to prevent mosquito breeding. No faith has been reposed in housing or nutrition, or any of the factors which constitute a high standard of living. It has been found 'difficult', as Barber said, to build houses so light and dry that *elutus* will

not enter them. Gametocyte control, mosquito-proofing, the organized application of larvicides, gambusia, and the radical elimination of breeding-places where possible has been the programme. There is left the possibility of biological changes in larval habitat and mosquito population which may in time reduce the labour and expense of perfection in mosquito control. Malaria still exists as I write, but the final victory is no longer in doubt.

It used to be said that we could do little or nothing for the scattered rural population of a malarious zone except to advise screening and to make quinine available at low cost. And whether a population is scattered or compact is still the most important local condition affecting the cost and hence the practicability of rural malaria control. It also influences the intensity of malaria. The smaller the unit of population, the more malarious it will be on the average. In a recent survey of Greece, M. C. Balfour discovered the following situation as between large and small communities:

	Spleen index	*Parasite index*
Urban localities (population over 1,000) . .	27·8	13·3
Rural localities (population under 1,000) . .	56·7	27·7

Where there is pressure of population on land, people must inhabit and cultivate malarious zones. It is, therefore, the poorest countries of Europe which have begun experiments in mosquito control covering a whole drainage area rather than limited to the environs of a centre of population. It was begun by Simic in the Kriva Palanka valley in Yugoslavia. The southern Slavs live dispersed upon their farms while the Italian and Greek peasants tend to concentrate in villages. Simic took a whole river valley and its tributaries as his unit of area and Paris-greening as his line of attack. Collins, Drensky, and Knipe have now controlled malaria transmission throughout the Strumitza valley in southern Bulgaria, comprising eleven villages and an important town,

Petritch. They have gradually but permanently eliminated, by skilful engineering and free labour, all the important breeding-places in the valley except the river itself, which is controlled with Paris green. Through this work the amount of arable land has been increased by 4,000 acres, and the double benefit to health and agriculture has justified the expenditure, which has been modest in proportion to its accomplishment. Greece has recently spent nine million pounds to reclaim 430 square miles of marshland and to protect another 430 square miles from inundation. In Italy the new programme of *grande bonifica* provides new land for an expanding population on a large scale.[1] In 1929, 5,600,000 acres were approved for hydraulic reclamation during a period of fourteen years and at an estimated cost of five milliards of lire. The law requires that the land be rendered habitable. This means that not only must the land be drained, but it must also be fenced, provided with proper houses, with water-supply and sewage disposal, and with roads, and the population given medical assistance, schools, football fields, and recreation centres. This is expected eventually to pay dividends, but in the meanwhile it is a successful solution of the rural malaria problem adopted by a poor country during a period of the greatest financial difficulty. It is pioneering with the first and second stage omitted. The same transformation of malarious marsh into healthy farmland has taken place more gradually and spontaneously in the Mississippi valley, where Le Prince estimates that there are now 110,000 miles of open ditch and 45,000 miles of tile drains.

If there is a conclusion to be drawn from this inadequate survey of malaria control to-day, it is that there is no justification for pessimism and inactivity in the face of the European or any other malaria problem. Ignorance,

[1] Longobardi, C., *Land Reclamation in Italy* (London, 1936), and Ilvento, A., *Quart. Bull. Hlth. Org. L.o.N.* **3** (2): 157, June 1934.

poverty, and disease constitute the vicious triangle of human social inadequacy. An attack on any one of them helps to dissipate the other two. But the causes of malaria, at least, are in the main independent of the ignorance and poverty of its victims and can be separately handled. It is easier to believe that release from the burden of malaria will help to bring prosperity and knowledge than that a higher standard of living and education must precede the eradication of malaria. The important fact is not that there are unsolved, and at present insoluble, problems of malaria in the world. It is that there are thousands of communities oppressed for ages by the disease that could be liberated with a little thought, energy, and money which would not be difficult nowadays to assemble and apply. The mechanism of malaria transmission is so complicated and delicate that it never has been able to resist any long-continued sabotage. Persistence is more important than perfection, and whether control is a partial failure or a partial success depends on the point of view. Above all, let us not allow ourselves to be discouraged by theorists, who, as Haslam says, 'adopt an attitude of detachment if not of scorn towards the work of those whose inclination and whose duty is to fight the disease *now* with weapons already proved useful, albeit imperfect, rather than to fold the hands while awaiting a problematical *therapia magna* of the future'.

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[mal.=malaria; (r.)= footnote reference]

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DEFINITIONS OF SOME OF THE SCIENTIFIC TERMS USED IN THIS BOOK

AMOUNT OF MALARIA: the percentage of infected individuals in the population.

Anopheles: a genus of mosquitoes with more than a hundred species, all infectible by the human malaria parasites, but only a few of which are *vectors* owing to habits and adaptations which bring them into frequent contact with man.

CARRIER (OF MALARIA): usually refers to an infected human being who 'carries' gametocytes in his blood and is infective to mosquitoes; the term *vector* is reserved for the mosquito.

CRESCENTS: male and female *gametocytes* (sexual forms) of *P. falciparum*, more sausage- than crescent-shaped.

DEVIATION: the diversion of mosquitoes from one host to another—see *zooprophylaxis*.

ENDEMIC MALARIA: that which persists in a community from year to year despite seasonal interruptions of transmission, or annual variations in intensity.

EPIDEMIC MALARIA: unusual prevalence in a community through introduction from without, or an exaggeration of the endemic amount due to climatic or other causes of an increased infection rate.

EURYGAMOUS: not a very good term for mosquitoes whose males swarm as a necessary prelude to mating (cf. *stenogamous*).

Falciparum: a species of *Plasmodium* causing so-called malignant tertian, estivo-autumnal, or tropical malaria in human beings, with daily febrile paroxysms and frequent early recrudescences. In the early stages it may cause 'pernicious' symptoms due to localization in the brain (Fig. 16, p. 155).

FLAGELLATE FORMS: motile, whip-like sexual cells liberated by the male gametocyte in the mosquito's stomach, which conjugate with the female parasite.

GAMETOCYTES: sexual forms of the malaria parasite found circulating at times in the blood-stream, which mate when drawn into the stomach of a mosquito and are the only forms which can infect a mosquito. The *micro-gametocytes* produce the smaller male cells, the *macro-gametocytes* the larger female cells, which conjugate in the mosquito's stomach.

GONOTROPHIC DISSOCIATION: dissociation of the nutritive and sexual functions so that a mosquito may continue to suck blood without producing eggs.

HYPERENDEMIC MALARIA: arbitrarily applied to situations in which at least half the children of the community or group give evidence of chronic enlargement of the spleen throughout the year.

INCUBATION: the period between the implanting of an infectious disease and its manifestation.

INTENSITY OF MALARIA: the average frequency of infections in a community; the transmission rate.

ISODIAGNOSIS: attempt to prove the existence of a latent infection by injecting a quantity of blood from the suspected case into a susceptible individual.

LEUKOCYTES: the circulating white corpuscles of the blood, some of which act as scavengers, increasing rapidly in number to defend the body against certain infections.

MACROPHAGE: Metschnikoff's name for the large wandering mononuclear phagocytic cells originating in reticulo-endothelial tissue.

Maculipennis: a complex anopheline species which is responsible for most of the malaria of Europe, with its principal races *atroparvus*, *labranchiae*, *messeae*, *melanoon*, *subalpinus*, and *typicus*, and the closely related *Anopheles elutus* of the Near East.

Malariae: a species of *Plasmodium* causing intermittent 'quartan' fever with paroxysms every fourth day (72-hour intervals)—a persistent infection which may relapse for years.

MAXILLARY INDEX: Roubaud's term for the number of teeth on the maxilla of the mosquito characteristic of a given species, race, or local form.

MEROZOITE: one of the spores formed by the segmentation or splitting up of the *schizont*, ready to infect a new red cell and become a *trophozoite*.

MICROCLIMATE: the physical conditions (temperature, humidity, illumination, &c.) immediately surrounding the individual, in a more or less restricted space or isolated environment.

MYELOCYTES: cells of the red bone marrow which give rise to certain leukocytes of the blood.

OOCYST: a cyst formed in the stomach wall of the mosquito by the fecundated female malaria parasite, which produces thousands of spores, and bursts when ripe, filling the salivary glands of the insect with infective parasites or *sporozoites* (see Fig. 21, p. 201).

OPSONIN: a substance developed in the blood-serum which by acting on micro-organisms or on red blood corpuscles makes them attractive to and more liable to be engulfed by phagocytes.

PARASITE INDEX: the percentage of persons in a population group or sample in whose blood malaria parasites are found.

PHAGOCYTES: fixed or free cells which remove foreign particles from the blood and destroy micro-organisms or harmful cells by enveloping and absorbing them.

Plasmodium: generic term for the malaria parasite, which is divided into several species, the commonest being *P. falciparum*, *P. vivax*, *P. malariae* of man; *P. knowlesi*, *P. inui*, *P. brasilianum* of the monkey; *P. cathemerium*, *P. praecox* of the bird.

RETICULO-ENDOTHELIAL SYSTEM: Aschoff's name for the cells of the network of tissue lining blood and lymph vessels and other blood channels and cavities of the body, which develop a common phagocytic behaviour towards foreign particles in the blood.

SCHIZONT: the asexual form of the malaria parasite which develops inside a red blood corpuscle, causing the symptoms of the disease, and multiplies by splitting into 8–15 spores, or *merozoites*.

SPLEEN INDEX: the percentage of persons in a population group or sample with palpably enlarged spleens.

SPOROZOITE: slender, spindle-shaped form of the malaria parasite produced by the *oocyst* (q.v.), and to be found in the salivary glands of an infective mosquito.

SPOROZOITE INDEX: the percentage of wild-caught anopheles females with malaria parasites in the salivary glands.

STENOGAMOUS: applied to mosquitoes which will copulate without swarming of the males (cf. *eurygamous*).

SUPERINFECTION: reinfection of an individual with the same strain of parasite which produced the previous infection.

THERAPEUTIC MALARIA: malaria infection intentionally induced for the cure of some pathological condition; malaria therapy.

TROPHOZOITE: early stage of the malaria parasite in the red blood cell. It is nourished by the cell and may become a *schizont*, multiplying by asexual division within the corpuscle, or a *gametocyte*, the sexual form, reproducing only in the mosquito.

VECTOR (OF MALARIA): any insect species known to transmit malaria in nature.

VIVAX: a species of *Plasmodium* causing so-called benign tertian malaria in human beings, with paroxysms every other day and long-term relapses over a period of 2 or 3 years (Fig. 17, p. 158).

ZOOPHILIC MOSQUITOES: those which bite animals in preference to man.

ZOOPROPHYLAXIS: the protection of man from biting insects by the creation of a 'barrier' of domestic animals to which the insects resort by preference for food.

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, OXFORD
BY JOHN JOHNSON, PRINTER TO THE UNIVERSITY